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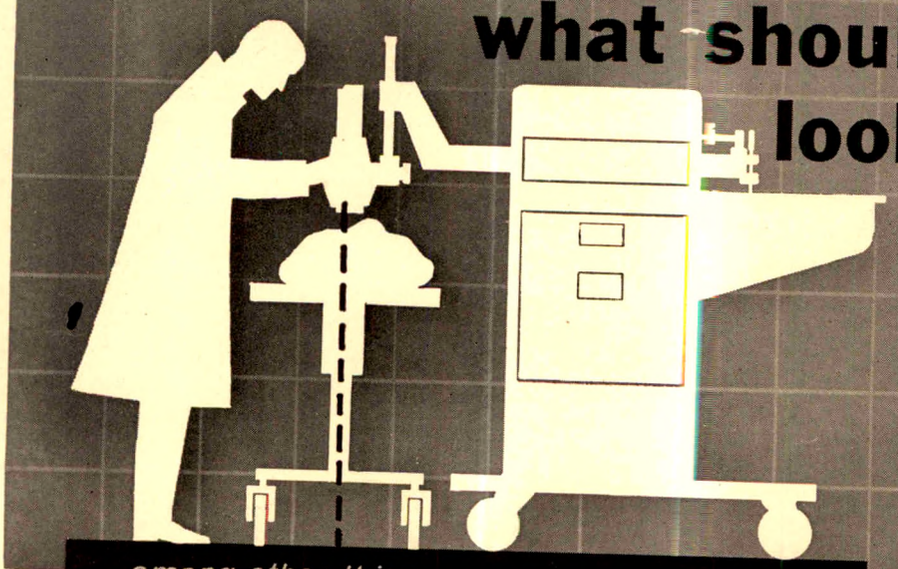
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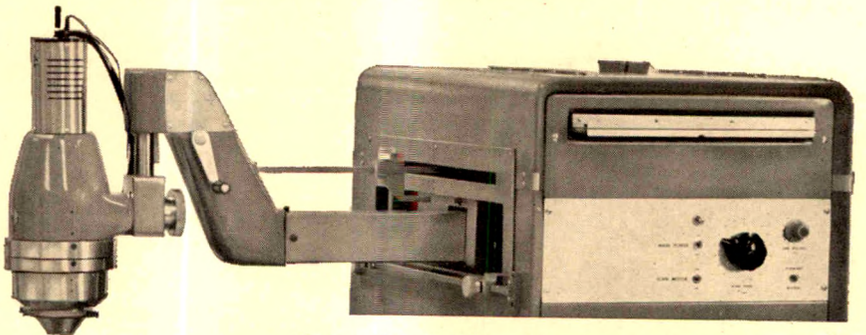


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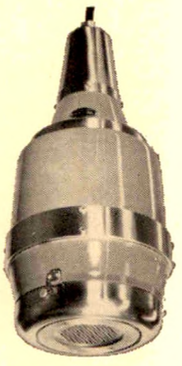
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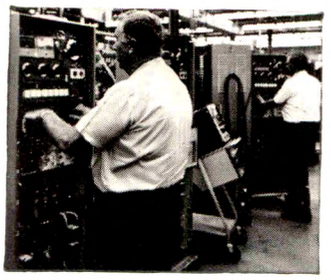
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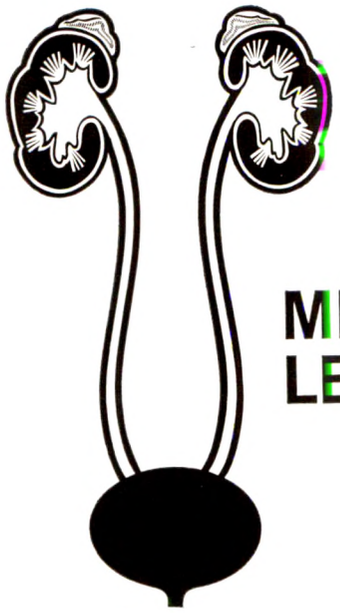
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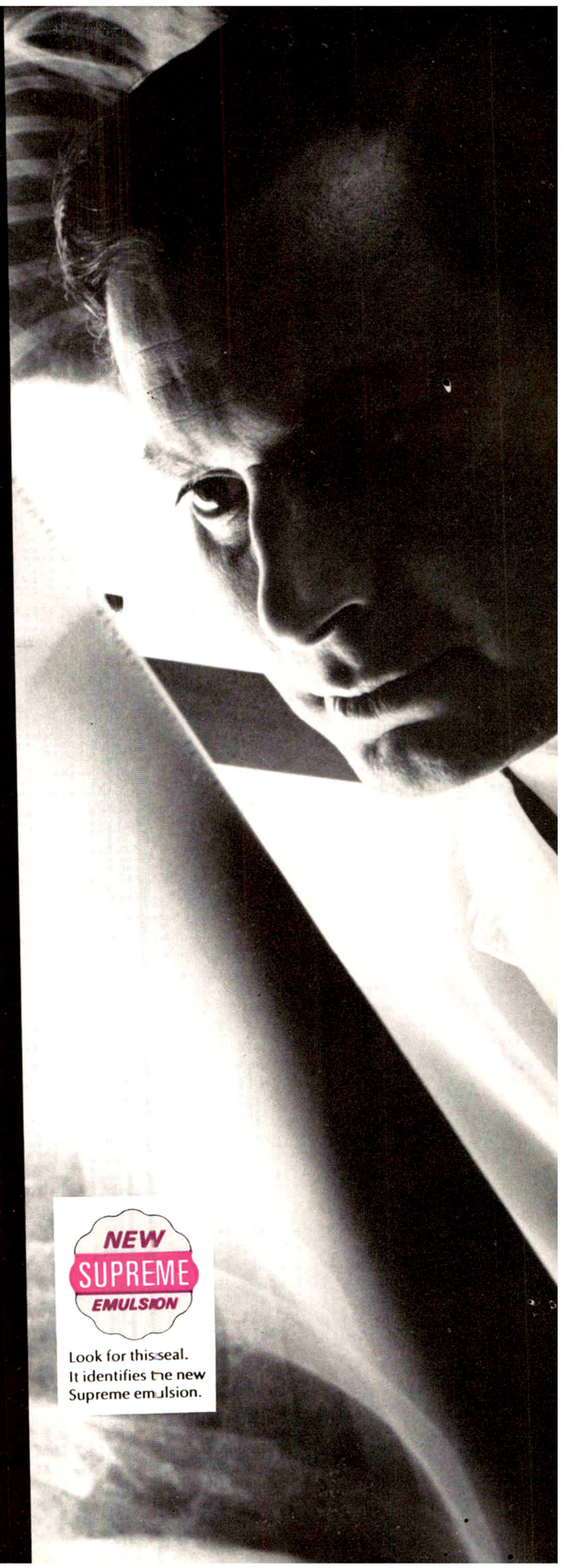
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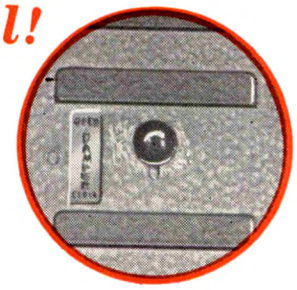
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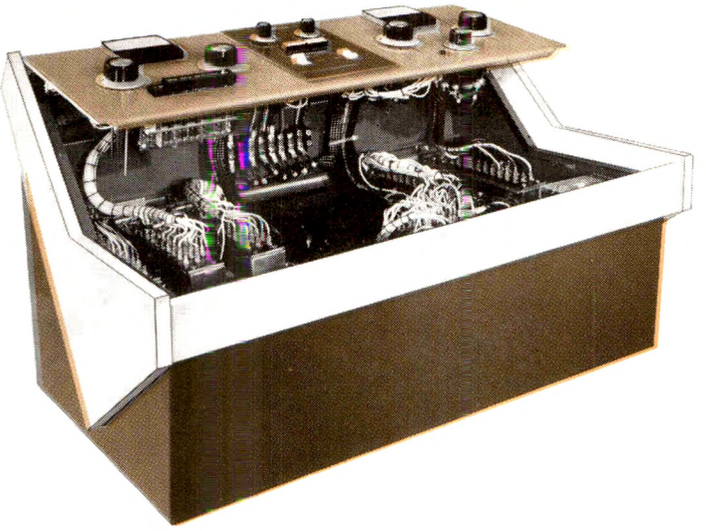
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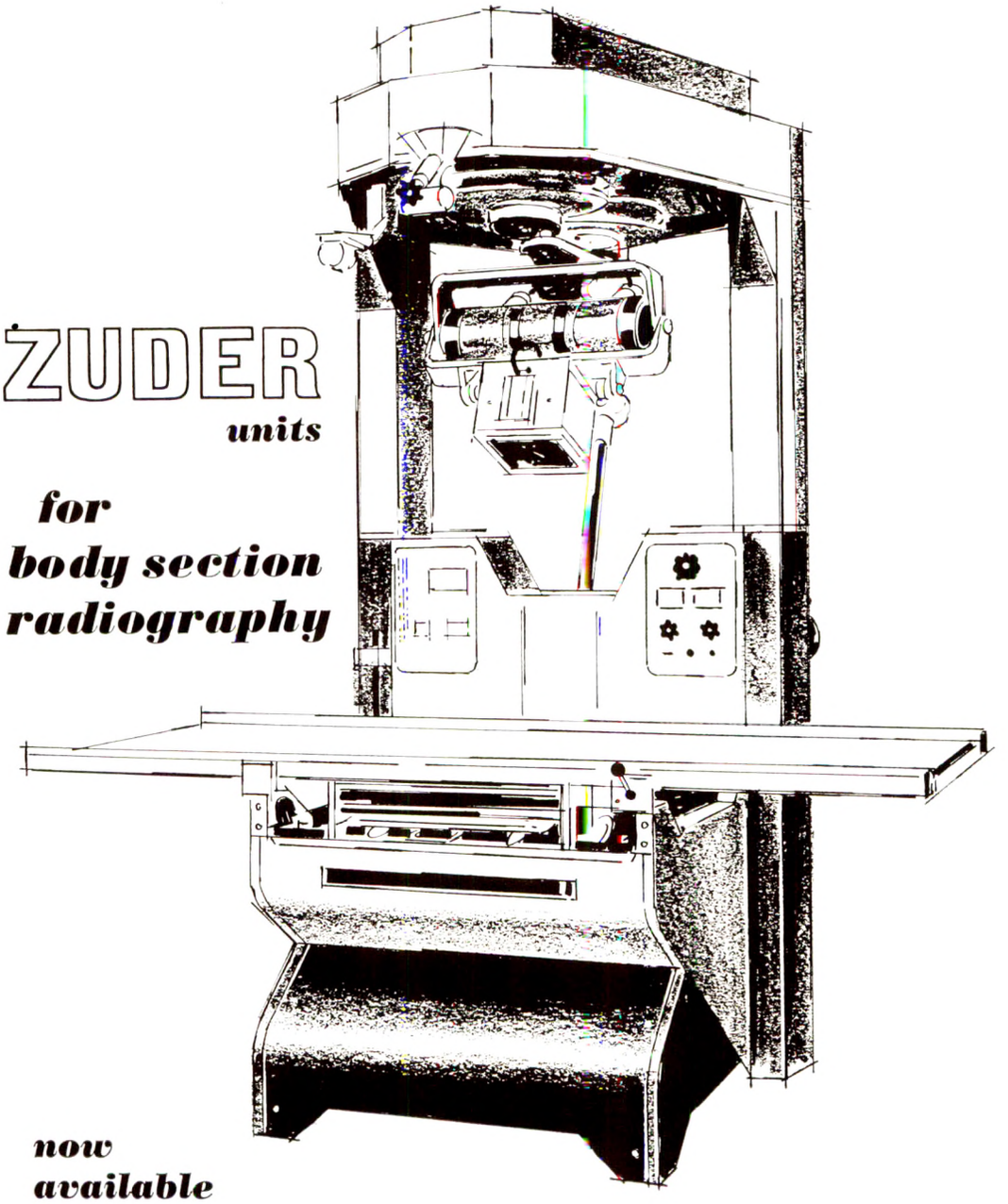
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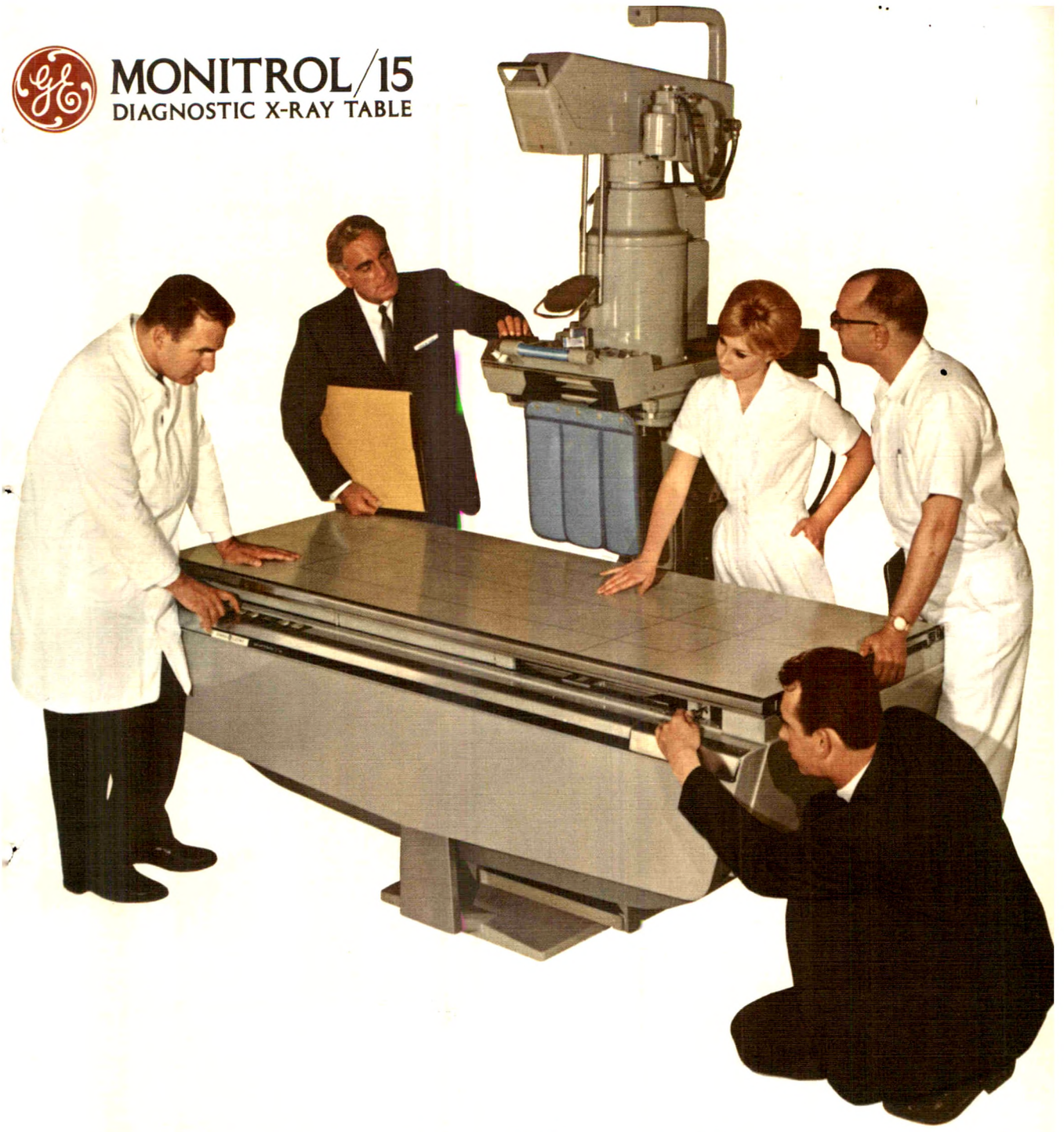
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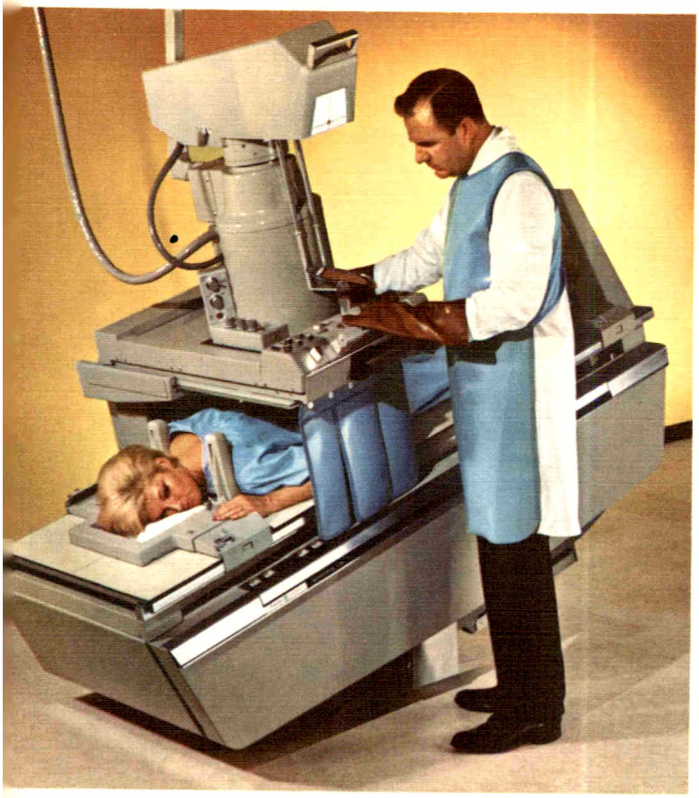
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Every newly-designed feature of the Monitrol/15 is aimed at easing the task of the radiologist. For instance—the fluoroscopic tower is lower and far lighter in weight to let you move it with minimum effort and park it faster. Result: a less fatigued radiologist at the end of every examination. Glide-back parking of the spot film device is standard and allows for easy patient positioning and fast table top clearance for radiography.

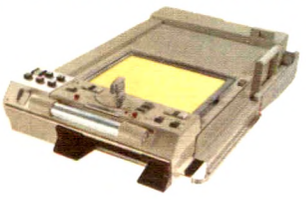
The Monitrol/15 accommodates the entire Fluoricon line of image intensifiers. The fluoroscopic beam is defined by the G-E True Field Collimator for improved quality spot film and fluoroscopic image. Collimator is controlled by a "servo-drive system" providing an automatic relationship between blade and control handle positions. Feature for feature, the Monitrol/15 offers more in patient comfort and operator convenience than any diagnostic table made today. It's a proud addition to the General Electric line of superior x-ray equipment.

Progress Is Our Most Important Product

GENERAL ELECTRIC

Radiologist-Designed Features for Total Diagnostic Performance

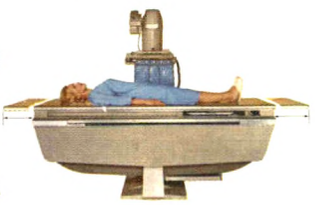
Spot Filming—Monitrol/15 accepts a choice of top loading, end loading spot film devices and the Fluoricon Pedestal. New low tower provides for spot film travel of 11-in. Distance from table top to underside of spot film device ranges 7-in. to 18-in.





Controls—Dual control is standard on the Monitrol/15. Controls are positioned for ease of access on both the table-front ledge and on the spot film device. The table-mounted switches are barium-proof.

Power Positioning—The moving table top with independent centering switch provides for a choice of table head-and-foot travel at installation—choose from 30-in. head/30-in. foot, 45-in. head or 45-in. foot travel.





We're equal to the occasion

with our new

THREE-POINT-FIVE film for 3½ minute processing

GEVAERT quality is so inherently good that it has taken just a minor adjustment of our emulsion formula to bring it into line for rapid processing.

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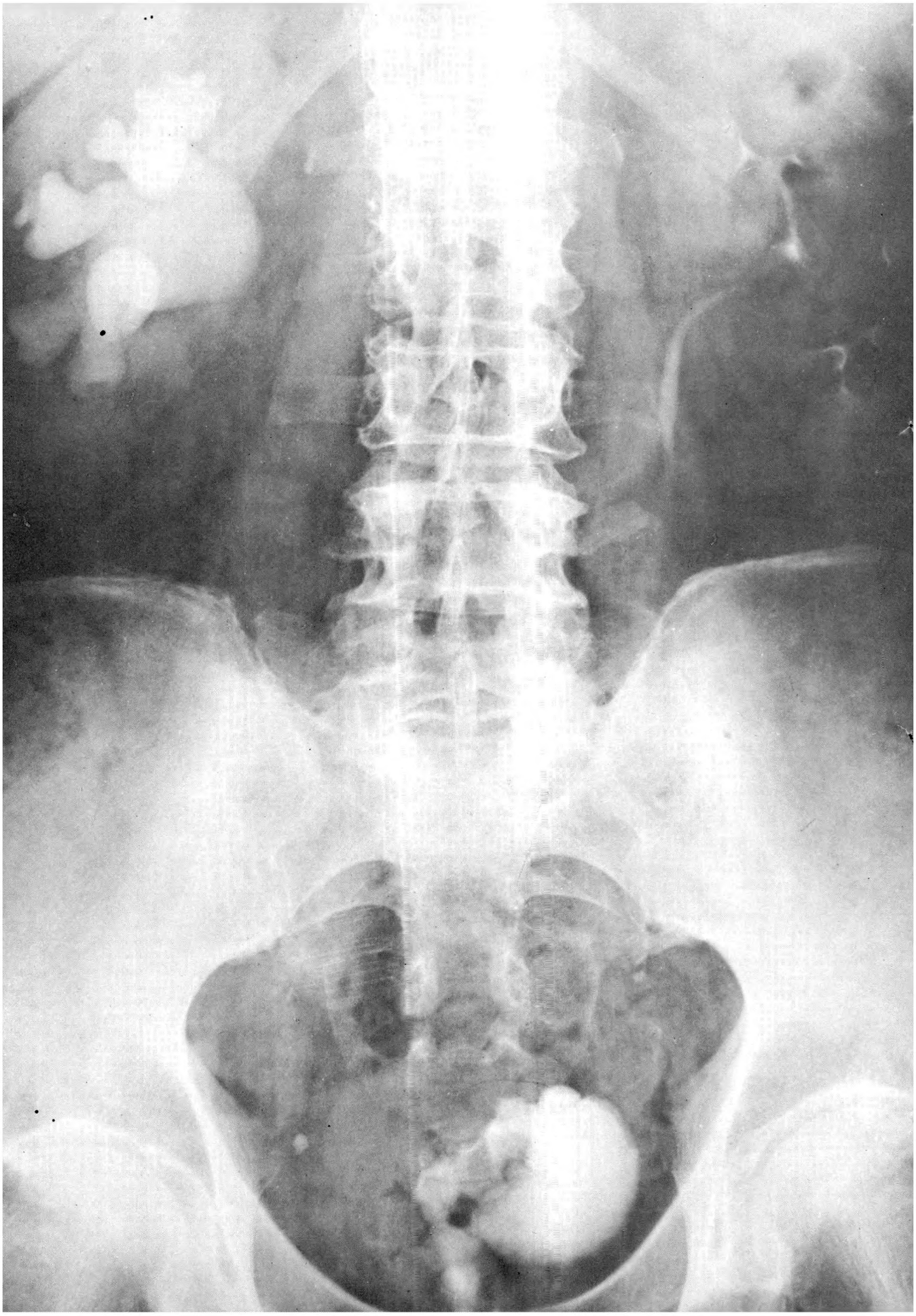
Contact your nearest GEVAERT representative. He'll be glad to advise you and make all arrangements for the changeover.

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Excretory urogram with Hypaque 50 per cent (30 cc.) Hydronephrosis, right, secondary to cancer of the bladder, blocking the orifice of the right ureter; 25 minute film.

when instrumentation is undesirable precise excretory urography

There are many patients where cystoscopy or catheterization is either undesirable or impossible in determining urinary tract pathology. This may be due to mechanical difficulties (e.g., deformity, anomaly, etc.), debilitated states, infancy, advanced age, infection, pregnancy or after extensive pelvic operations.

In such cases, Hypaque Sodium 50% often provides precisely defined urograms of the kidneys, ureters and bladder, with valuable information about their functional activities, undisturbed by instrumentation. Further advantages are: (1) no age limit to the procedure, and (2) no need to administer an anesthetic.

Contraindications: Advanced renal destruction associated with severe uremia, and multiple myeloma.

Precautions: Caution is advised in patients with hyperthyroidism, hypertension, severe cardiovascular disease, active tuberculosis, and a history of asthma or other allergy, especially to iodine. Because of the possibility of temporary suppression of urine, it is wise to allow an interval of at least 48 hours before repeating retrograde or excretory urography in patients with unilateral or bilateral reduction of normal renal function.

Side effects: Excretory urographic agents may produce symptoms of an anaphylactic* nature in sensitive persons. Patients should be watched carefully during injection as serious reactions, including fatalities, have occurred with all commonly used mediums. Minor reactions, such as nausea, vomiting, excessive salivation, flushing, dizziness, urticaria, and muscular twitching may occur. Infrequently "iodism" (salivary gland swelling) appears two days after exposure and subsides by the sixth day. In euthyroid patients following excretory urography with Hypaque, protein-bound iodine is elevated and the thyroid I^{131} uptake is lowered, returning to normal after the 3rd and 4th days respectively.

Supplied: In sterile aqueous solution, Ampuls of 30 cc. (with 1 cc. test ampuls), boxes of 1, 10 and 25. Also, rubber stoppered vials of 20 cc. and 30 cc., boxes of 1, 10 and 25.

*Physicians should study the package insert for information on preventive measures and management of untoward reactions *before* administering Hypaque (diatrizoate sodium).

Urograms with excellent anatomical detail

Hypaque® 50%
sodium

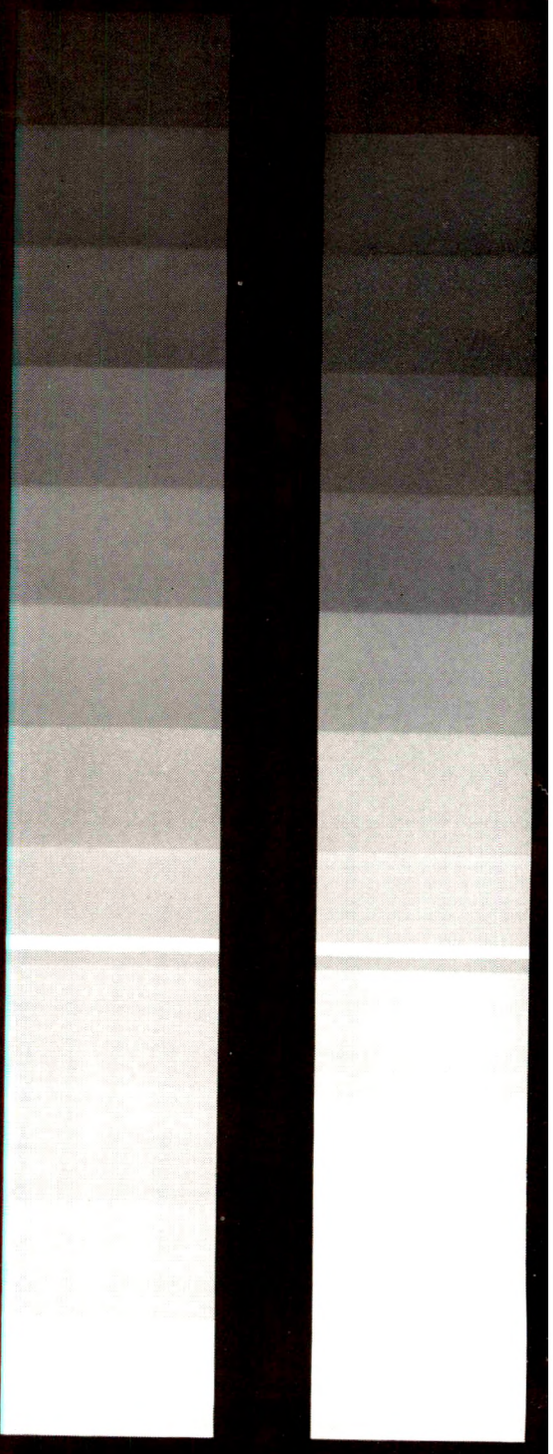
brand of **sodium diatrizoate**

an illustrated booklet with complete information is available by writing to Winthrop Laboratories

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Du Pont focuses its science and energy on Diagnostic Clarity



You can use CRONEX* 2 DC whether you like contrasty radiographs, or softer images with less contrast.

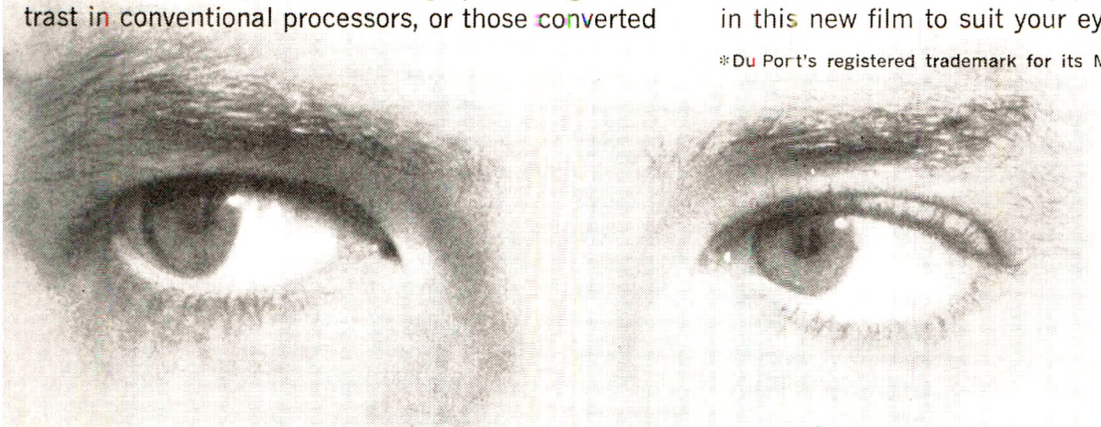
The reason?

This new film can be processed to give results anywhere between the two extremes of contrast represented by the step wedges at left.

CRONEX 2 DC produces radiographs of high contrast in conventional processors, or those converted to Double Capacity with developer temperatures around 92° F. The softer look, the longer gray scale and the increased latitude come when you lower temperatures in the converted processor to about 86° F. and make compensating increases in exposure.

Your Du Pont Technical Representative can demonstrate the contrast range available to you in CRONEX 2 DC, and can help you adjust the contrast in this new film to suit your eyes.

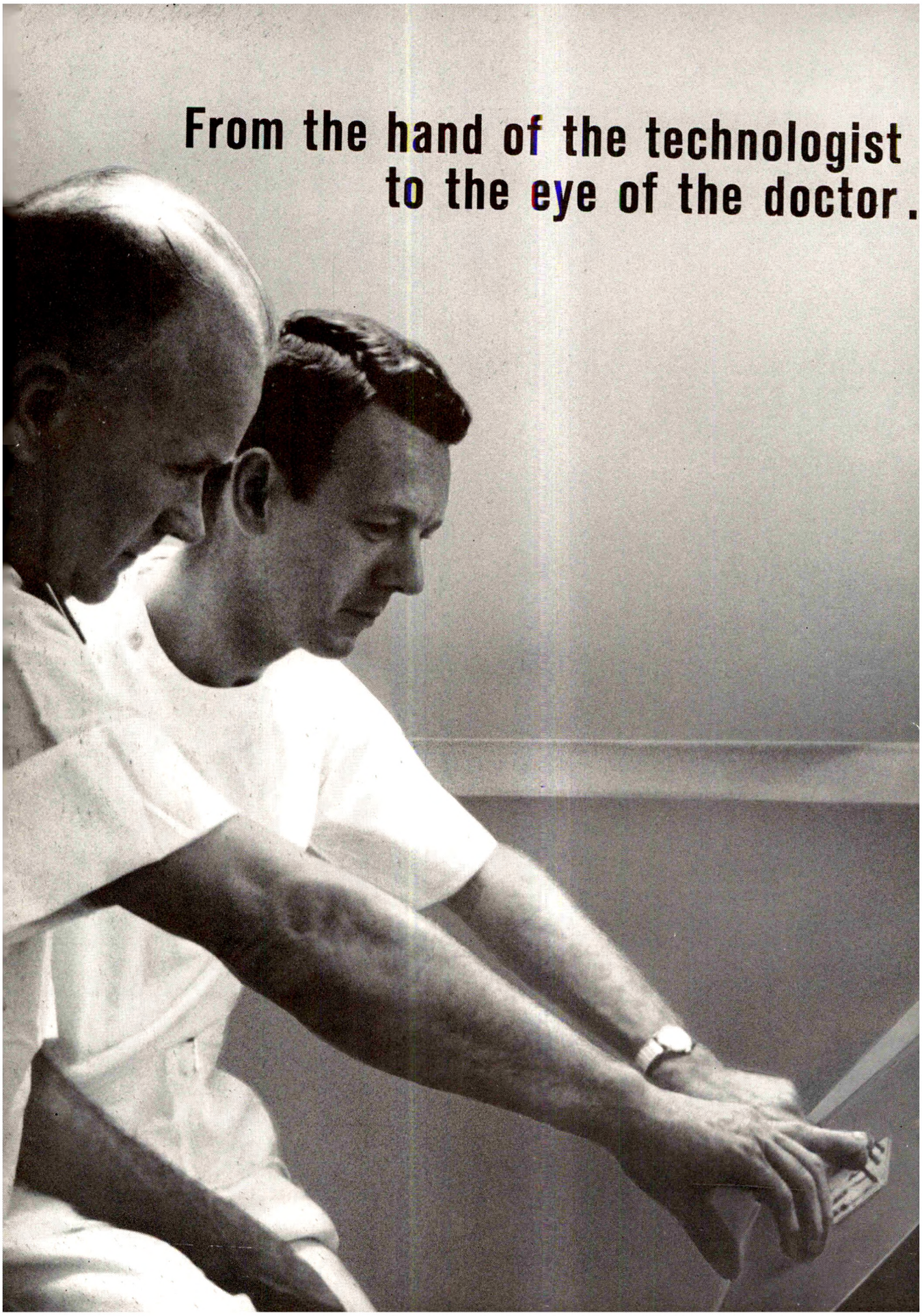
*Du Pont's registered trademark for its Medical X-ray film.



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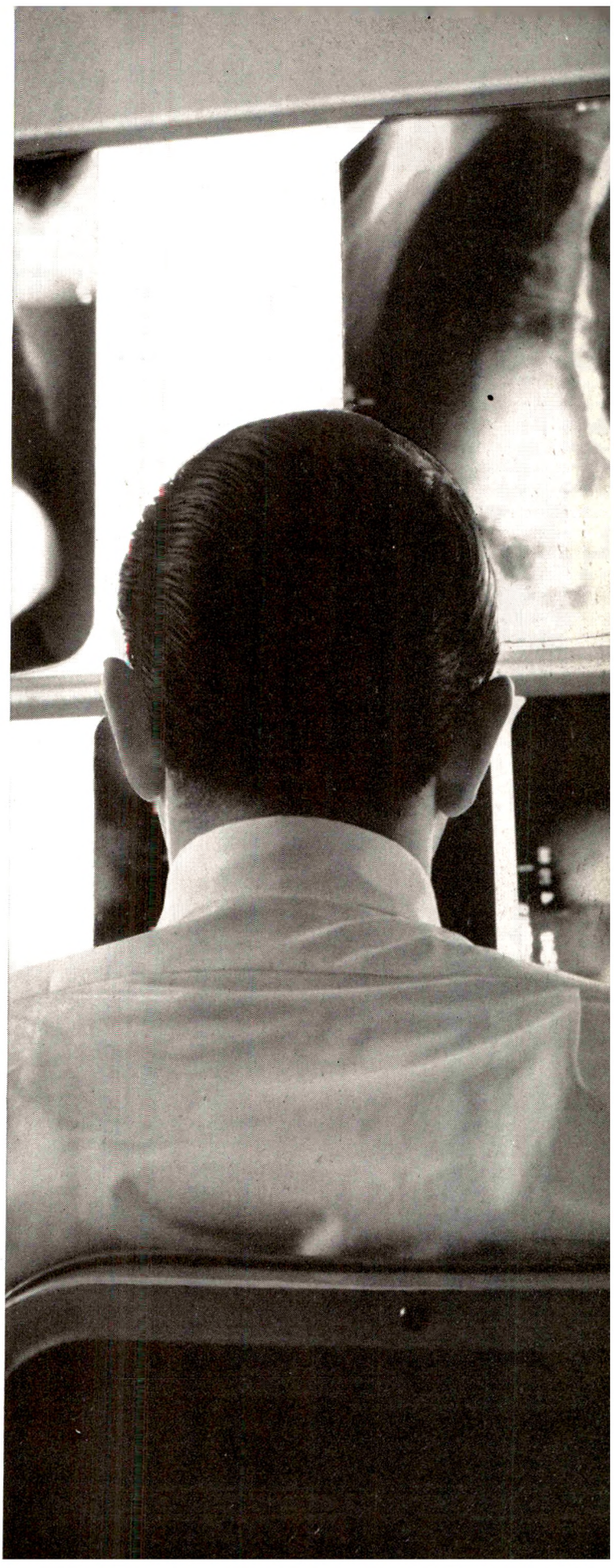
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M-96



"...[pulmonary embolism] may exist in a grave form for a considerable time without objective signs being present on physical examination or routine chest films."[1]

Pulmonary embolism is a mimic. Because its symptoms resemble those of other cardiorespiratory diseases—particularly myocardial infarction[2,3] and pneumonia[4]—investigators have long sought simple and certain methods of diagnosing it.

Many diagnostic clues—but often no clinical picture

Until a few years ago diagnosis depended primarily on the clinical history, physical findings, chest films, electrocardiograms, angiography, and pulmonary function studies. Each of these was helpful. Sometimes not even *all* of them were conclusive.

Surgery, prolonged immobilization, metastatic carcinoma and trauma often precede pulmonary embolism—but are not necessarily followed by it. Pain, dyspnea, hemoptysis may signal pulmonary embolism—but they aren't necessarily peculiar to it. The electrocardiogram may be normal in spite of it.[5] And there is no pathognomonic radiographic picture of pulmonary embolism.[5]

To be clinically valuable, however, a new diagnostic test should meet two criteria:
1. it should be correlated with known pathology; i.e., it should be carefully compared with other diagnostic procedures;
2. it should offer information not attainable as easily or as safely by accepted tests.[6]

Pulmonary arteriography meets the first criterion and is a most reliable diagnostic tool. It is, however, a time-consuming procedure and one that requires experienced personnel.[2]

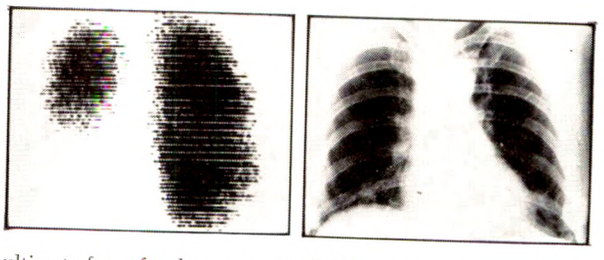
"...lung scintiscanning can detect an obstruction of the pulmonary circulation as soon as it is established."[7]

Not only is the diagnostic procedure of lung scanning both safe and easy,[2] but there is information that is not attainable on chest films. "...it appears that the lung scan can point to the site of the embolic lesions before signs of lung infarction are recognizable on plain chest films."[1]

The scan and the x-ray shown confirm this statement.* The photoscan of this female patient, aged 58, was taken August 13, 1965 with Albumotope-LS (Squibb Aggregated Radio-iodinated [I^{131}] Albumin [Human]). Pulmonary emboli are clearly evident. The x-ray, taken the same day, shows no radiographic evidence of pulmonary emboli.

Lung scanning meets both criteria for a clinically valuable diagnostic test. Findings are correlated with pulmonary function studies, angiography, pathology and the clinical state of the patient. And, scanning with Albumotope-LS has been proven to be "simple, rapid, and safe in the diagnosis, localization and ultimate fate of pulmonary emboli."[2] But the lung scan should not be relied upon as the only diagnostic procedure in the diagnosis of pulmonary embolism.[1]

*Illustrations furnished through the courtesy of George V. Taplin, M.D., Harbor General Hospital, Torrance, California.



Dosage and Scanning Procedures: Recommended scan doses of 150 to 300 microcuries of Albumotope-LS (Squibb Aggregated Radio-iodinated [I^{131}] Albumin [Human]) depending on the instrumentation available and the technics employed. Scanning can immediately follow administration of slow intravenous injection or be delayed up to 1 to 1½ hours depending on preferred technic.

Side Effects and Precautions: Extensive clinical use of Albumotope-LS has not borne out the hypothetical possibility that particles of large size might induce deleterious cardiovascular or cerebrovascular effects. No antigenic properties have been specifically related to this product; one patient with a known history of angioneurotic edema, who had been given Lugol's solution in conjunction with aggregated radio-albumin similar to Albumotope-LS, developed urticaria.

Radioisotopes should not be used in pregnant women, nursing mothers, or in patients under 18 years of age unless indications are very exceptional.

Available: As a sterile, non-pyrogenic, aqueous suspension. Each cc. contains approximately 1 mg. aggregated human serum albumin labeled with 800-1500 microcuries of iodine-131 at time of manufacture. Also contains 0.9% benzyl alcohol as a preservative.

References: 1. Haynie, T. P., et al.: J. Nucl. Med. *6*:613, 1965. 2. Sabiston, D.C., Jr., and Wagner, H.N.: Ann. Surg. *160*:575, 1964. 3. Cooley, R.N., and Donner, M.W.: Am. J. M. Sc. *247*:601, 1964. 4. Wagner, H.N., et al.: New England J. Med. *271*:377, 1964. 5. Hinshaw, H.C., and Garland, L.H.: Diseases of the Chest, ed. 2, Philadelphia, W. B. Saunders Co., 1963, pp. 438-9. 6. Dworkin, H.J., et al.: Michigan Med. *64*:829, 1965. 7. Quinn, J.L., et al.: Radiology *82*:315, 1964. 8. Taplin, G.V., et al.: Health Physics *10*:1219, 1964.

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to see evidence of pulmonary embolism *before* it appears on chest films

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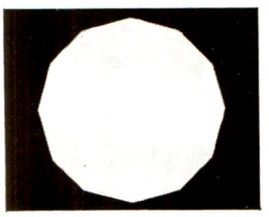
'The Priceless Ingredient' of every product is the honor and integrity of its maker

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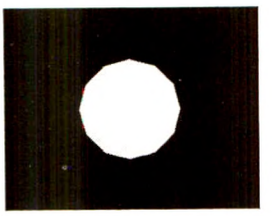
collimaster

This is Machlett-Videx Round/Rectangular Collimation:

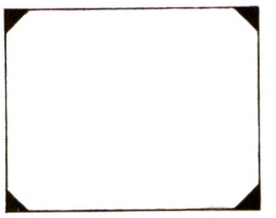
Any Geometry Without Attachments



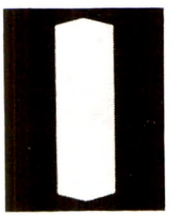
Routine
image areas
(gall bladder)



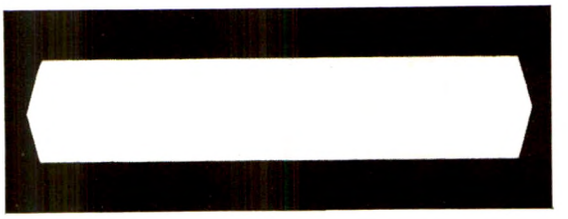
High definition
image areas
(sinus & mastoids)



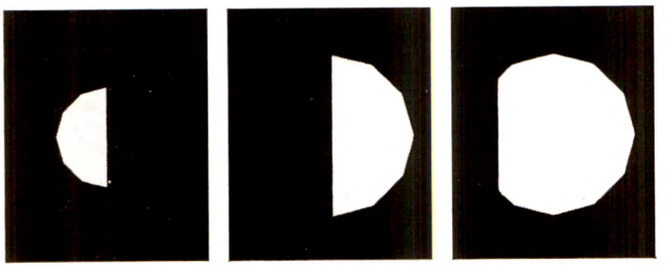
Typical large
area coverage
(abdomen)



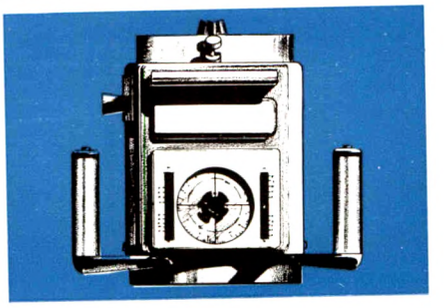
Selective
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with Telepaque you can depend on your cholecystogram

visualization → functioning gallbladder
nonvisualization → gallbladder disease*

Numerous studies with large numbers of patients show a diagnostic accuracy ranging from 95 to 100%

Baker and Hodgson[1] of the Mayo Clinic and Mayo Foundation, reporting on a series of 1,207 cholecystographic examinations with TELEPAQUE in which all diagnoses were subjected to surgical and pathological verification, found 98 per cent of all the diagnoses were correct. *All* the nonvisualized gallbladders were found to be diseased, and the "increased accuracy of this diagnosis seemed to have a direct relationship to the medium employed". (The authors emphasize, however, the primacy of correct technical procedure and vigilance by the radiologist over the particular contrast medium used.)

Alderson[2] found TELEPAQUE 99 per cent accurate in cholecystography of 315 patients. He concluded that "TELEPAQUE is held to be the most satisfactory for routine radiological investigation of gallbladder symptoms". Six other groups of investigators have published similar results with TELEPAQUE which varied in accuracy from 95 to 100 per cent.[3-8]

only with Telepaque is such diagnostic accuracy so substantially documented

References: 1. Baker, H. L., Jr., and Hodgson, J. R. (Mayo Clinic and Mayo Foundation): Further studies on the accuracy of oral cholecystography, *Radiology 74*:239, Feb., 1960. 2. Alderson, D. A. (King's College Hosp., London): The reliability of Telepaque cholecystography, *Brit. J. Surg. 47*:655, May, 1960. 3. Rogers, J. V., Jr., Bonmati, J., Leigh, T. F., and Gay, B. B., Jr. (Emory University Hospital, Atlanta): Correlation of radiographic and surgical findings in gallbladder disease, *J.M.A. Georgia 42*:489, Nov., 1953. 4. Tillinghast, A. J. (New York); X-ray diagnosis in disorders of the biliary tract, *Rev. Gastroenterol. 20*:750, Oct., 1953. 5. Mauthe, H. (St. Agnes Hosp., Fond du Lac, Wis.): The accuracy of X-ray examination of the gallbladder, *Wisconsin M.J. 53*:473, Sept., 1954. 6. Garland, L. H. (San Francisco): New techniques in cholecystography, *Minnesota Med. 39*:433, July, 1956. 7. Whitehouse, W. M. (University Hospital, Ann Arbor, Mich.): Correlation of surgical pathology with Telepaque cholecystography in doses of two grams, *Surg., Gynec. & Obst. 100*:211, Feb. 1955. 8. Dietz, M. W., and Litton, L. D. (Springfield, Mo.): Syllabus of cholecystography, *GP 14*:109, Oct., 1956.

*An extraordinary high degree of accuracy has been achieved with Telepaque in studies involving large series of patients; however, unusual causes of nonvisualization other than gallbladder disease also exist.

Dosage: The TELEPAQUE tablets (0.5 Gm. each) are preferably administered from 10 to 12 hours before the time scheduled for cholecystography. At about 10 P.M., 6 tablets should be swallowed, each with one or two mouthfuls of water (with a total of a full glass of water). In patients where visualization of the extrahepatic ducts is especially indicated, from 10 to 12 tablets have been recommended. In patients with thin or normal build, weighing less than 150 pounds 4 tablets may prove sufficient.

Side Effects: TELEPAQUE has low toxicity, and side effects when they occur are usually mild. Gastrointestinal effects (diarrhea, cramps, nausea, vomiting) are the most common. Usually the diarrhea is mild, consisting merely of a few loose stools, although in isolated cases it may be severe. Other side effects reported include dysuria, headache and, on rare occasions, skin rash, urticaria, pruritus, and flushing.

Contraindications: Acute nephritis, uremia, and gastrointestinal disorders that prevent absorption of the medium.

Supplied: Tablets of 500 mg., envelopes of 6 tablets, boxes of 5 and 25 envelopes; also bottles of 500.

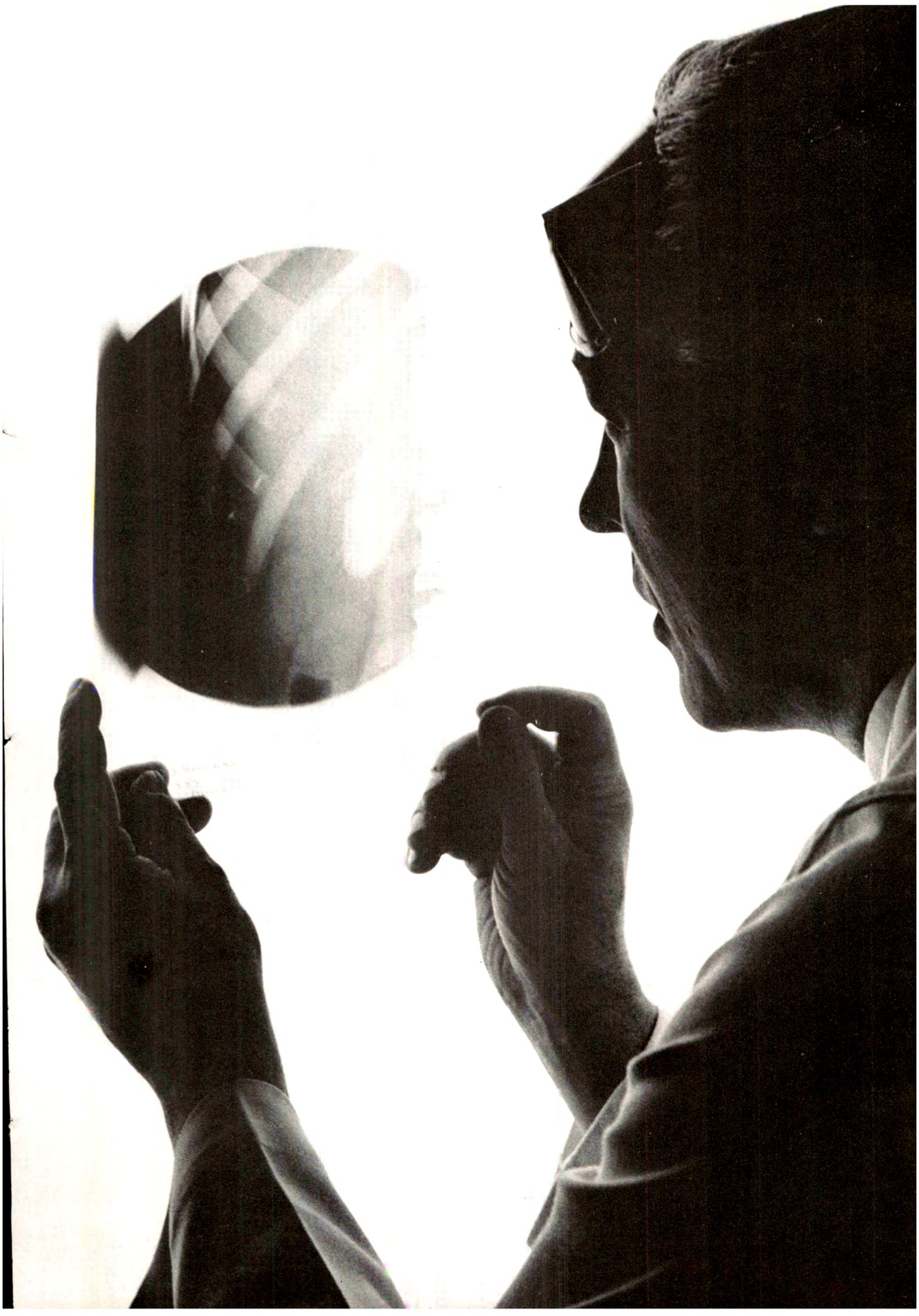
CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION

Telepaque® for precise oral cholecystography and cholangiography

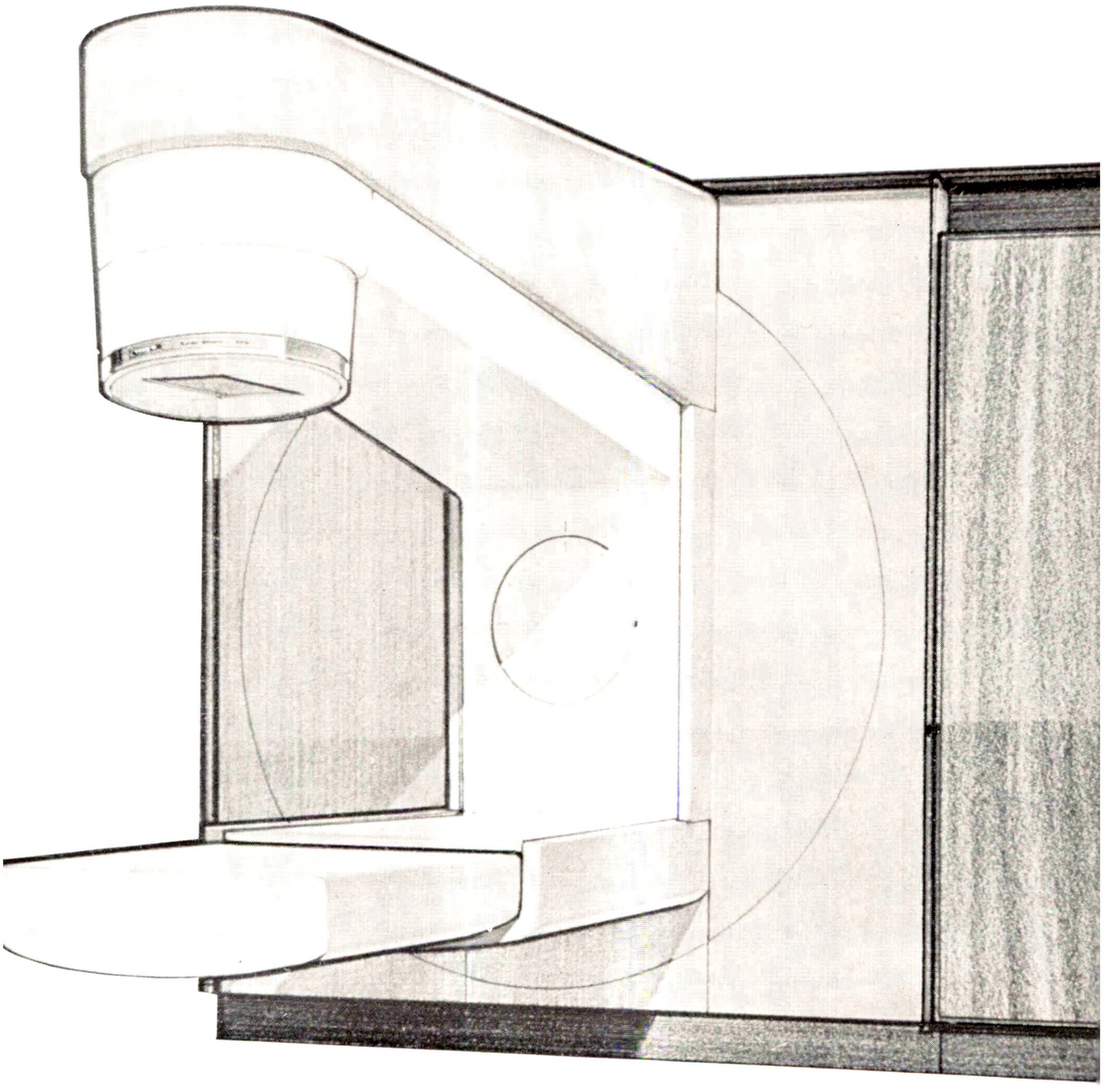
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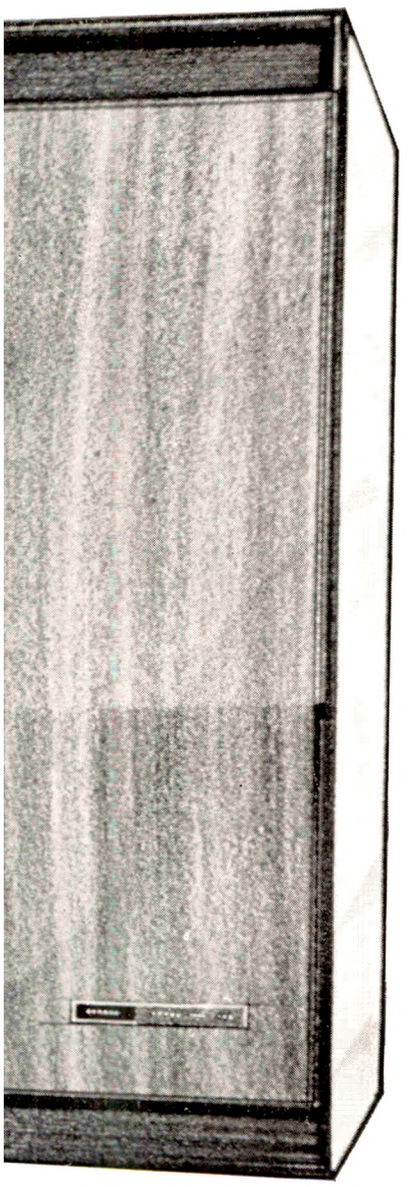


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The Mevatron 8 is the first medical linear accelerator that not only speeds routine fixed or rotary therapy, but also gives you the ability to perform advanced therapy and research using high X-ray outputs, the electron beam, or neutron production. You get an energy range of 3–10 MeV, with energy levels push-button selectable in 1 MeV steps.

Advanced Therapy High X-ray output and the retractable beam shield on the Mevatron 8 make it especially useful for techniques such as hyperbaric oxygen therapy and whole body irradiation. Its wide energy range and its capability for increased depth dose allows treatment of deep seated tumors with fewer fields. Electron therapy is especially effective because of the minimal X-ray contamination of the beam (less than 0.1%).

Examples of associated therapy techniques include management of advanced cases of mycosis fungoids and Kaposi's Hemorrhagic sarcoma. You'll also find it easier to perform post-operative treatment of the rib cage and other areas where only skin penetration is involved, because the wide energy range of the Mevatron can be precisely controlled.

Research and Experimental Uses In addition to the many therapy uses of the Mevatron, you also get a unique research capability, to help you spread your initial investment over a broader range of productive functions. Examples include demonstration and investigation of radiation effects on medical, physical, and biological systems and the performance of in-vivo and in-vitro radiation studies.

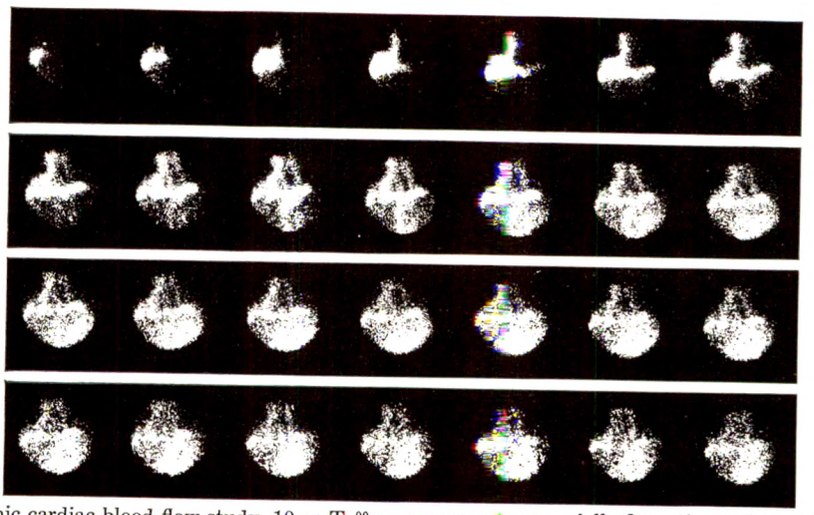
You can also use the Mevatron to produce neutrons, thus providing short-lived radioisotopes for analysis, diagnosis and therapy. Additional uses of the Mevatron include bone and tissue sterilization and the bulk sterilization of sutures and other hospital supplies.

Complete Planning Assistance The Mevatron 8 is the most versatile medical linear accelerator available today, and to make sure that you get the maximum effective use from your investment, Applied Radiation has a strong program of assistance. Numerous experts within the company, and qualified consultants, can help you plan every step of the linear accelerator installation, from initial financing considerations through installation and complete therapy and research program planning.

For a more detailed discussion of the therapy/research capabilities of the Mevatron 8, write or call Applied Radiation in Walnut Creek, California.

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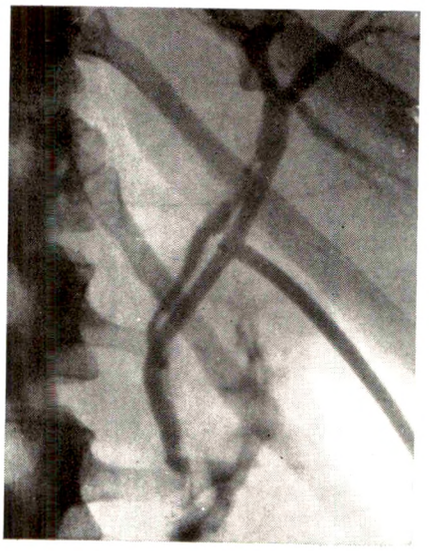
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MEDOPAQUE — The medium of choice in hysterosalpingography, cholangiography (operative and t-tube), biliary ducts, fistulous tracts, postoperative empyemic cavities and soft tissue sinuses.

Aqueous and viscous, Medopaque is absorbed completely from serous and mucous surfaces, in 45 minutes to an hour following instillation. Presents no problems of residual contrast medium in body cavities or interference with subsequent examinations. Non-toxic in the event of intravasation, Medopaque is completely safe if refluxed into the vascular system.





Medopaque is miscible with body secretions, wets and spreads well without droplet formation. Visualization is optimal, net iodine content comprising 20%, w/v. Supplied sterile in 10cc. vials, rubber-stoppered and metal-sealed.

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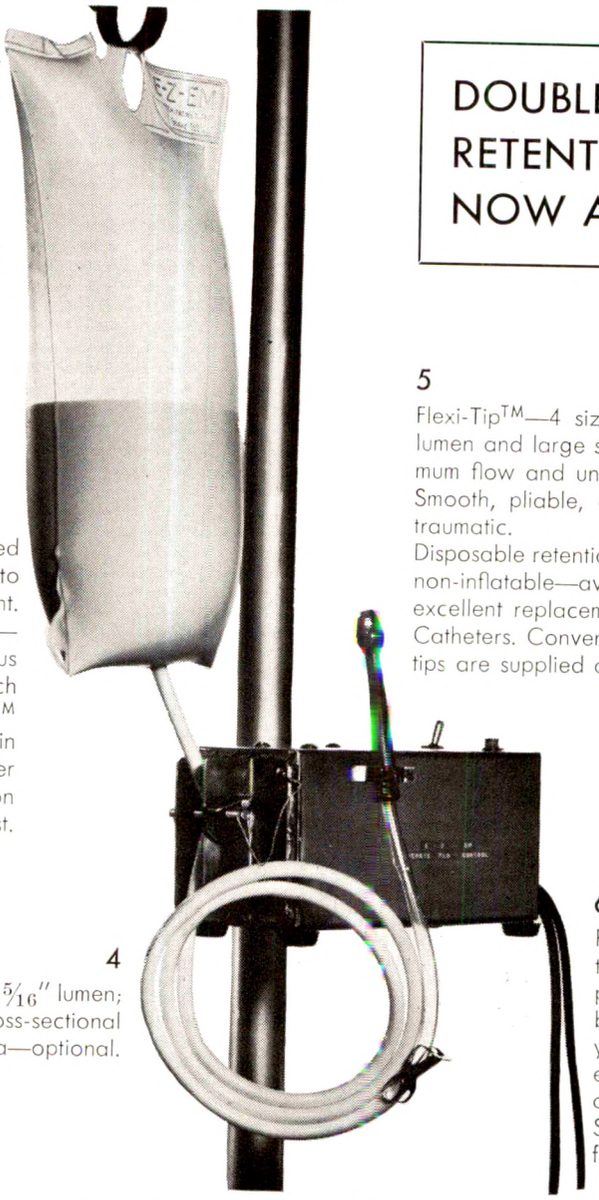
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J. ARNOLD BARGEN, M.D.
Caldwell Lecturer, 1966

THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 99 JANUARY, 1967 No. 1

INTRODUCTION OF CALDWELL LECTURER, 1966

By F. J. L. BLASINGAME, M.D., EXECUTIVE VICE PRESIDENT OF THE AMERICAN MEDICAL ASSOCIATION

The speaker chosen to give the Caldwell Lecture tonight has been an effective man. His effectiveness has resulted from a generous combination of intelligence, energy, compassion, and honesty, along with other characteristics which have brought him renown and respect.

He possesses a pleasing and warm personality; he is easy to know. Other people are comfortable in his presence; he is one of them—unassuming, free of ostentation. His courage and strength are such that he never needs to place his goods in the show-window for exhibition. His open, forthright manner allows others to see and appreciate his qualities.

His effectiveness has been demonstrated consistently in a number of ways.

He has been an effective teacher. As Dr. Clyde A. Stevenson, one of the many students of the speaker, recalled, "He has written his name indelibly across the pages of gastrointestinal literature and has become nationally and internationally acclaimed for his knowledge and contributions concerning the medical aspects of colon disease." His influence as a teacher, directly and indirectly, has been profound.

His effectiveness can be judged further by his development and use of new knowledge which he has readily passed on to others through his treatment of patients, his contacts with his fellow physicians and others working in the health field, and by his extensive writings.

Limitation of time allows only a brief review of his effective life.

J. Arnold Bargen became Dr. Bargen in 1921 upon graduation from the Rush Medical College of the University of Chicago. Prior to his entry into Rush College, he had received a Bachelor of Science degree at Carleton College in his home state of Minnesota.

His internship was served at Chicago's St. Luke's Hospital, following which service he was named a John J. Borland Fellow in Medicine at that institution for the years 1922 and 1923.

In the latter year, he joined the Mayo Clinic in Rochester, Minnesota, where, for a period of 37 years, he built an enviable reputation as a physician and teacher and made many of the outstanding contributions to medicine which have so clearly fitted him for the honor he is receiving tonight.

Starting at the Mayo Clinic as first assistant in the Section of Medicine in 1923, he became instructor in medicine at the Mayo Foundation Graduate School, University of Minnesota, 2 years later. The next year, he was appointed to the clinic staff and was named assistant pro-

fessor in 1931. Four years later he was associate professor; and in 1942 he became head of a Section of Medicine.

In 1948 he became Professor, and 8 years later, in 1956, was elevated to Chairman of 4 Sections of Medicine and President of the staff of the Mayo Clinic.

He retired from the Mayo Clinic on January 1, 1960, having earned the right to rest, and having discharged any obligation a person carries into this world to make a significant contribution to its betterment. However, inactivity was not for this man.

On June 1 of his retirement year, he joined the Scott and White Clinic in Temple, Texas, as Senior Consultant in Gastroenterology at the Scott and White Memorial Hospital and the Scott, Sherwood and Brindley Foundation, also of Temple. On July 1, 1963, he was appointed Director of Medical Education.

His various medical affiliations, impressive as they may be, have been combined with positions of responsibility in many of these organizations.

For example, as a member of the American Medical Association, he served as Chairman of its Council on Scientific Assembly from 1963 to 1965. In 1949 he was President of the American Gastroenterological Association; in 1955 he was President of the Minnesota State Board of Medical Examiners; and in 1957 served as President of the Minnesota State Medical Association. For 10 years, starting in 1947, he was an AMA Delegate from Minnesota, and now holds valued membership in the Texas Medical Association, Bell County Medical Society, American College of Physicians, Texas Academy of Internal Medicine, and the Texas Society of Gastroenterologists and Proctologists.

In addition, he is a member of the medical advisory boards of both the National Foundation for Research in Ulcerative Colitis and the Sears-Roebuck Foundation. He was President in 1964 of the Interstate Postgraduate Medical Association of North America.

The honor he is receiving tonight is by no means the first significant recognition that has come to him. Since 1960, the Mayo Graduate School of Medicine has granted an annual "J. Arnold Bargen Award" for the best research project in gastroenterology by a Foundation Fellow. In 1957 he received the Distinguished Service Medal of the Minnesota State Medical Association; and he was Chairman of judges for the 1963–64 International Science Fair.

He is the author or co-author of 4 books in the field of his specialty and has been guest editor of 2 special publications: a gastroenterology issue of the Mayo Clinic's "Postgraduate Medicine," in 1959; and of a special issue of the Scott and White Clinic publication of that same name in 1966.

The list of his published articles through September, 1965, totals 379, a number of which have appeared in languages other than English.

Such a man, then, is our speaker and guest of honor. But, even these facts fail to tell us the whole story of this man. They tell us of certain of his accomplishments and of the efforts of ourselves and others to pay him honor. Kindling of our imagination is required if we are truly to see the character, the devotion, the dedication to high principles that lodge in the soul of such a man and motivate him to live so effectively.

How blessed is medicine that he chose it as a profession! How blessed is mankind to be able to enjoy the fruits of his labors!

He is honored by us tonight; but, in truth, he honors us.

I am pleased to have the privilege of presenting the 1966 Caldwell Lecturer, who will tell us a story that no man could tell as well, as he addresses us on his topic, "Chronic Ulcerative Colitis: Diagnostic and Therapeutic Problems. A Lifelong Study."

I am proud to present to you, J. Arnold Bargen.

* * *

Vol. 99, No. 1

CHRONIC ULCERATIVE COLITIS: DIAGNOSTIC AND THERAPEUTIC PROBLEMS; A LIFELONG STUDY*

CALDWELL LECTURE, 1966

By J. ARNOLD BARGEN, M.D.†
TEMPLE, TEXAS

CHRONIC ulcerative colitis is a disease which usually begins at the anal canal and spreads relentlessly orad, eventually to involve the entire large intestine and frequently the distal ileum. At times, long stretches of the distal ileum are inflammed, but the most severe changes generally are in the rectum and the descending colon. I have spent much of my professional life studying this disease which has had many other names. Words such as *idiopathic* and *nonspecific* frequently have been added to indicate the seriousness of the colitis. The German literature is filled with discussions of *colitis ulcerosa gravis*.

When chronic ulcerative colitis is considered, one must remember that the disease may begin in segments of the large intestine other than the rectum.[3] Hence, in recent years, terminology such as *granulomatous colitis* has been suggested for the condition previously referred to as *regional* or *segmental ulcerative colitis*. Although any segment of the large intestine may be involved by this form of colitis, 51 per cent of the lesions were limited to the transverse colon in a group of 201 patients seen at the Mayo Clinic.[1] At one time, the entity was called *right-sided colitis* by Dr. Burrill B. Crohn[4] who with his colleagues believed that the process was found most commonly or almost entirely in the right colon. As experience grew, however, this condition was found to involve any segment of the large intestine above the rectum and, at times, even the ileum.

A discussion of *regional enteritis* will be avoided at this time because those who have had rather extensive experience with regional enteritis and with ulcerative colitis consider these as two separate entities. At times, and particularly among our colleagues in Great Britain, regional enteritis has been given a physician's name.* This, in turn, has been applied to lesions in the colon, and the name has referred to both regional enteritis and a form of *segmental colitis*. Segmental colitis exists as a granulomatous or an ulcerative disease; and the instances of granulomatous colitis constitute a small percentage of the entire group of individuals harboring the disease entity called ulcerative colitis.

A typical roentgenogram of the common form of ulcerative colitis shows a narrowing and shortening of the colon with an absence of haustra in the involved segment. During the acute and fulminating phase, numerous areas of mucosa are denuded leaving islets of mucosa in the remainder of the large intestine. Frequently, these islets of mucosa are mistakenly called polyps. The roentgenologist may report *extensive ulcerative colitis with secondary polypoid degeneration*. This is an incorrect designation because real polypoid degeneration has not occurred. Mucosal denudation has resulted in the development of secondary mucosal tags, or so-called pseudopolyps (Fig. 1, *A–E*).

The purpose of the author is to discuss the serious nature of chronic ulcerative colitis and the problems which may be associated when the disease is uncontrolled.

* Crohn's disease.

* Presented at the Sixty-seventh Annual Meeting of The American Roentgen Ray Society, San Francisco, California, September 27–30, 1966.

† Emeritus Professor of Medicine, Mayo Graduate School of Medicine, Rochester, Minnesota; Senior Consultant in Gastroenterology, Scott and White Clinic; and Director of Medical Education, Scott and White Memorial Hospital and Scott, Sherwood and Brindley Foundation, Temple, Texas.

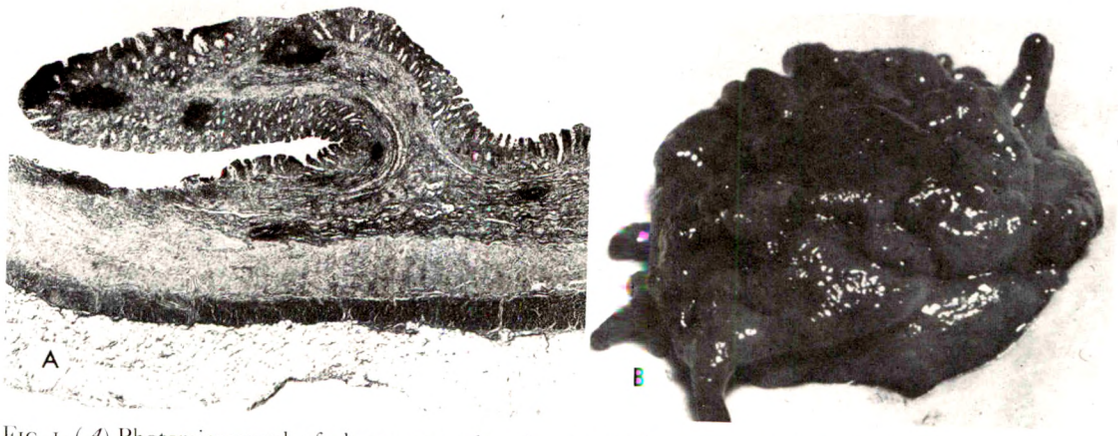


FIG. 1. (*A*) Photomicrograph of a large mucosal tag in a resected segment of colon. (*B*) Photograph of mucosal tags on the exposed mucous membrane of a colonic stoma.

When the diagnosis of chronic ulcerative colitis is made (and it should be made early), active and vigorous treatment must be instituted to control the condition and to avoid the many unpleasant complications. Because this audience of radiologists, naturally, is intent on picking up diagnostic pearls, you are not too interested in how or why the structure of the large intestine changes after treatment. Therefore, treatment will be mentioned only when the diagnostic pattern of a given case of chronic ulcerative colitis is altered.

GENETIC CONSIDERATIONS

The familial incidence of chronic ulcerative colitis is low. The disease has occurred in several members of the same family, and some workers have thought that 10 per cent of their cases were familial. However, when the clinical records of the first 2,000 patients with chronic ulcerative colitis

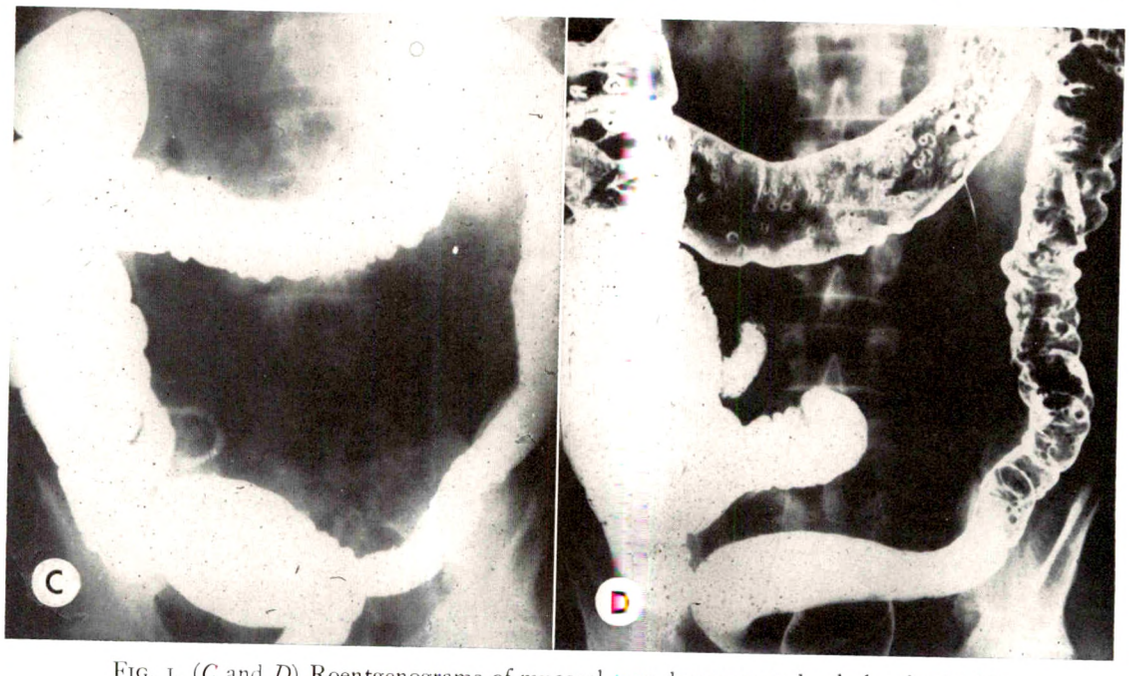


FIG. 1. (*C* and *D*) Roentgenograms of mucosal tags demonstrated only by the double contrast method for examining the colon.

who came to the Mayo Clinic were reviewed, only 26 familial instances were found.[5] The condition occurred in 5 members of one family, 2 sisters and 3 brothers. In several families with 2 children, both children had ulcerative colitis. Two brothers who had slept together since infancy developed the disease: one had surgical treatment, whereas the other's colitis was controlled medically. Ulcerative colitis has occurred in twins. It may occur in blood relatives, but a sex-linked gene has not been proved. The process has occurred in mother and son and in father and daughter when they were closely associated. A most impressive familial instance occurred in a mother and daughter. In 1954, the mother came to me with severe ulcerative colitis which involved the major portion of her large intestine. The lesion was most advanced in the left half of the colon, with a stricture in the descending colon. In 1965, I saw her daughter, then a senior in college. She had the same type of severe disease involving the same segment of bowel with a stricture in the same location. Except in a man and a woman who had ileac stomas prior to their marriage, ulcerative colitis has not been observed after marriage to a partner who has had ulcerative colitis. Bloody diarrhea has been noted in an infant whose mother had ulcerative colitis.

CLASSIFICATION

Early in my studies of chronic ulcerative colitis, I classified patients with the disease into three main groups: (1) those with the so-called insidious colitis which was rather mild but progressive; (2) those with the more severe form with accompanying diarrhea, bleeding, and some fever; and (3) those with the fulminating disease, a very serious and, at times, lethal condition.

Even in its milder form, the colitis can be regarded as a serious, devastating, and possibly a disabling disease. Whether the condition is a mild proctitis or an advanced destructive entity, as is frequently the case, it invariably is accompanied by great anxiety and concern because one of its chief

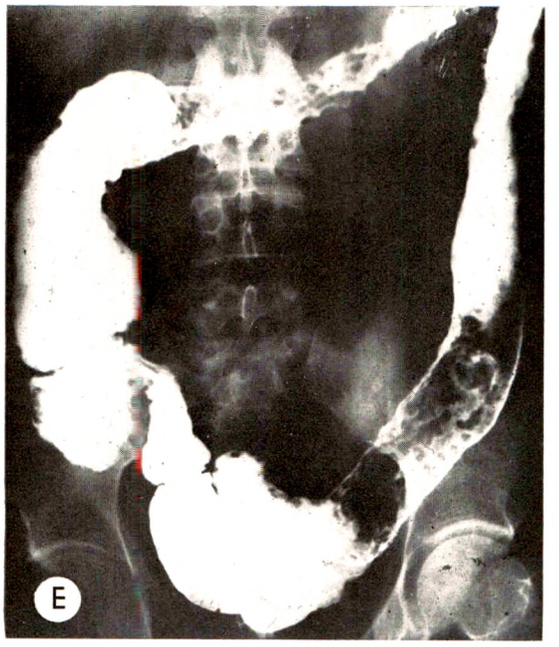


Fig. 1. (*E*) Roentgenogram illustrating extensive areas of denuded mucosa which simulate polyps.

features is the passage of blood from the rectum. This, whether it occurs as mild bleeding or massive hemorrhaging, is a fearsome complication.

COMPLICATIONS

Unfortunately, the numerous systemic features of chronic ulcerative colitis make the designation of a disease with systemic lesions of colonic origin particularly applicable. In such a devastating condition, one might also expect many local complications. This is indeed the case. These localized complications and sequelae readily divide themselves into three groups: (1) conditions which primarily are medical problems, (2) conditions which may be medical problems but later develop surgical implications, and (3) conditions which present primary surgical problems (Table 1).

GROUP 1. CONDITIONS WHICH PRIMARILY ARE MEDICAL PROBLEMS

The ocular involvement in chronic ulcerative colitis includes conjunctivitis and episcleritis, but sometimes the retina, the optic nerve, and all of the other ocular

TABLE I

COMPLICATIONS AND SEQUELAE OF CHRONIC ULCERATIVE COLITIS

GROUP 1. Conditions which primarily are medical problems.
- a. Ocular involvement
- b. Arthritis
- c. Pyoderma gangrenosum
- d. Circulatory disorders
- e. Massive hemorrhage
- f. Biliary cirrhosis
- g. Pseudoinfantilism
- h. Pregnancy
- i. Unwise use of adrenocortical hormones

GROUP 2. Conditions which may be medical problems but later develop surgical implications.
- a. Rectal stricture
- b. Stricture of the colon above the rectosigmoid region
- c. Perianal and rectovaginal fistulas
- d. Intra-abdominal fistula and perforation of the bowel
- e. Mucosal tags mistaken for polyps
- f. Massive hemorrhage
- g. Toxic dilatation of the colon
- h. Perforation

GROUP 3. Conditions which present primary surgical problems.
- a. Intra-abdominal fistula
- b. Stricture above the rectosigmoid
- c. Perforation of the large intestine
- d. Pseudopolyps or mucosal tags which enlarge
- e. Toxic dilatation
- f. Secondary carcinoma
- g. Pseudoinfantilism

layers are involved. I recall one young man who had many complications which primarily were medical problems. Complete uveitis which began as conjunctivitis affected his eyes, and he became totally blind. In addition, he had disabling arthritis. Only one arm could be moved slightly at the elbow. Mentally, he was alert, but physically he was totally disabled. Finally, his disease became so extensive that total colectomy was necessary. In most instances, however, the secondary conjunctivitis and the more extensive episcleritis respond readily to mild adrenocorticosteroid ointments and instillations.

Secondary arthritis is a complication which occurs in about 5 per cent of the patients with ulcerative colitis. Patients, of course, may have ulcerative colitis coexisting with arthritis, the one disease quite independent of the other. However, the arthritis of ulcerative colitis is rather unique. My former colleague, Dr. Philip S. Hench often spoke of a distinct form of rheumatoid arthritis which he designated as the arthritis of ulcerative colitis. In this form of arthritis, the synovial membranes have such a characteristic appearance that they can be identified roentgenographically. Evidence of irritation may be substantiated by withdrawing fluid from the synovial joint.

Another condition which is not difficult to diagnose is pyoderma gangrenosum. Its onset and progression are of great importance. The lesions begin as erythema nodosum, perhaps, on one of the shins; and they may spread to other parts until the human body is involved from scalp to toe. Although the lesions begin as erythema nodosum, they disintegrate to form small abscesses in 24 to 72 hours. These, in turn, form ulcers which may spread rapidly. Roentgen therapy has been used without much success, and aluminum subacetate solution (0.5 per cent), applied as a wet dressing, has been about as satisfactory as any available therapy. All useful liquid adrenocorticosteroids have been applied. Triamcinolone, injected at the periphery during the early stage of a lesion or soon after the skin breaks down, has been of real value. The reason for emphasizing pyoderma gangrenosum is because the pyodermic lesions frequently are a mirror image of what is going on in the patient's large intestine. As the colitis heals, the pyodermic lesions usually heal, and their recession is parallelled by the recession of the colitis. In controlling pyoderma gangrenosum, the objective is the concomitant vigorous treatment of the ulcerative colitis itself.

At a recent conference on the newer biologic concepts in ulcerative colitis sponsored by the Digestive Disease Foundation,

the altered circulation in patients with ulcerative colitis was discussed. It was pointed out that the rate of blood flow is not the same in patients with ulcerative colitis as it is in persons with normal colons —and that the rate varies at different age levels. Phlebitis of the extremities is a frequent complication of ulcerative colitis, but major vessels seldom are occluded. Perhaps, this condition is related to the vascular activity of blood transport in the patients who have severe ulcerative colitis because phlebitis occurs only during fulminating or severe disease, when the abdominal aorta and both renal vessels have become occluded.

Bleeding is a pathognomonic sign of ulcerative colitis, and I believe that I can say without fear of contradiction that unless bleeding occurs, the patient does not have the form of ulcerative colitis which begins in the rectum. Diffuse and severe bleeding to the point of massive hemorrhaging is uncommon however, and the cause of such bleeding frequently can be determined by checking the prothrombin time. This value may be increased if the liver is damaged. Administration of antibiotic agents that change the bacterial flora of the intestine may play a part in the bleeding; also, severe denudation of the mucous membrane must receive consideration. If massive hemorrhaging occurs in a patient whose prothrombin time is within normal limits, a good plan is to administer additional vitamin K, to instill warm starch solutions or, in some instances, to instill barium as an enema for diagnostic purposes. The barium instillation should be administered slowly without distending the colon.

Biliary cirrhosis is not an uncommon complication of long standing ulcerative colitis, and I have wondered why it does not occur more often. When a group of 32 colitis patients who were hospitalized consecutively were studied at the Mayo Clinic,[6] liver damage of varying degrees of severity was found. In 9 patients, the liver was infiltrated excessively with fat. Six patients had chronic pericholangitis, 2 had diffuse hepatitis, 1 had hepatic necrosis, 6 had biliary cirrhosis, and 3 had metastatic adenocarcinoma.

When ulcerative colitis attacks a child during the first decade of life or before he reaches 5 years of age, the growth of the child is affected and a seriously underdeveloped youngster results unless the disease is controlled. Not infrequently, patients with this form of ulcerative colitis have been mistakenly diagnosed to have pituitary infantilism rather than failure to develop because of a severe destructive disease. I have seen young persons in their early twenties who have not acquired their secondary sexual characteristics which should have evolved in their mid-teens. I have seen boys with high pitched voices who were without pubic or axillary hair, and 17-ketosteroid excretion was at low levels. Roentgenographic studies of such patients will demonstrate the underdeveloped epiphyses of the bones and, of course, the typical changes in the colon.

A difficult problem from the diagnostic as well as the therapeutic standpoint concerns the pregnant woman who has or has had ulcerative colitis. The association of pregnancy with ulcerative colitis often presents an enigma. A woman with severe ulcerative colitis may inadvertently become pregnant and the colitis will become quiescent in the second trimester and will remain so until the baby is delivered. Conversely, a woman may have had colitis, and the inflammation has healed. When she becomes pregnant, a severe exacerbation of the condition may occur during the second trimester of her pregnancy. Once the pregnancy has progressed beyond the second month, the roentgenographic diagnosis becomes complicated and many other difficult features enter into the examination and care of the pregnant woman with ulcerative colitis. If the woman who has had her colon removed because of ulcerative colitis becomes pregnant, great problems may arise. The intestine may prolapse through the ileac stoma, and massive hemorrhaging may severely reduce the blood prothrombin level. Two reasons for these adverse conditions might



FIG. 2. (*A*) Photograph illustrating the severe peripheral edema associated with profound hypoproteinemia in a 22 year old man.

be the absent colon and the damage to the liver.

In the treatment of patients with ulcerative colitis, one of the major tragedies has arisen from the inadvertent and excessive use of adrenocortical hormones. Early studies concerning the use of cortisone indicated that patients were benefitted temporarily. These studies were based on the fact that in patients with advanced ulcerative colitis, particularly in the younger age group, the excretion of 17-ketosteroids and of adrenocorticosteroid hormones was greatly reduced and sometimes absent. Hence, improvement might be expected from the administration of adrenocorticosteroids. That these substances should be used only to tide the patient over a serious complication, or a serious episode of the disease, has become apparent however, and they should be discontinued as soon as possible. Unfortunately, adrenocorticosteroid therapy has not always been discontinued, and some of the most serious complications have followed. If the patient has received an adrenocorticosteroid preparation for a long period of time, he has become dependent upon this medication. Hence, weaning him from the excessive use of the steroid agent may be a major problem.

The following case illustrates the difficulties which may arise from the long term use of adrenocorticosteroid hormones. A young man, aged 22 years, had a rather severe form of ulcerative colitis for 6 years. He had taken Prednisone (U.S.P.) without interruption for more than 4 years. When he came under my care, he was in a marked state of depletion. His total serum protein level was 2.5 gm.; albumin, 1 gm., and globulin, 1.5 gm. He had severe peripheral edema and profound hypoproteinemia (Fig. 2*A*). His outstanding problem was a peculiar filling defect in the large intestine. A deformity, suggestive but not characteristic of a neoplastic lesion, was noted at the hepatic flexure (Fig. 2, *B–E*). His condition was such that surgical treatment could not be justified. Since the initial administration of the Prednisone (U.S.P.) a favorable change had not occurred and his hemoglobin level had gradually decreased. Episodes indicating perforation had not occurred. The young man failed progressively and died. At postmortem examination, a perforation with a pericolic abscess was demonstrated. A silent perforation, one without any clinical signs, had occurred.

GROUP 2. CONDITIONS WHICH MAY BE MEDICAL PROBLEMS BUT LATER DEVELOP SURGICAL IMPLICATIONS

Frequently, patients with ulcerative colitis have a network of flimsy, cobweb-like structures which fill the rectum. The rectum is so involved that the physician has

difficulty in determining which passage is the rectal lumen when he passes his finger into the rectosigmoid. This type of stricture can be dilated readily. Also, somewhat firmer definitely inflammatory strictures can be managed when dilatation is repeated every 7 to 10 days, or sometimes oftener. Such dilatation is accomplished best as the colitis heals and as a result a satisfactory rectal ampulla may develop (Fig. 3, *A* and *B*). If the nature of a stricture at the rectosigmoid or beyond this region cannot be determined by digital or proctoscopic examination and a neoplastic lesion seems possible, surgical investigation is in order.

Some workers have stated that strictures do not occur in patients who have the usual form of ulcerative colitis, that this complication occurs only in those with the so-called granulomatous colitis. This has not been true in my experience. I believe that strictures may occur in any patient with ulcerative colitis—particularly with involvement in the rectum and in distal segments of the large intestine.

Anal crypts become infected, and the resulting perianal fistula may present serious and painful problems. Such a fistula should be treated gingerly. The colitis should be treated actively, but the fistula should not be disturbed except, perhaps, for superficial opening of the abscesses. After the colitis heals, the fistula may be repaired satisfactorily. Occasionally, a rectovagina fistula develops. If surgical treatment is attempted during active disease, a cloaca may occur. Fistulas above the rectum, resulting from localized, slow perforation into the neighboring viscera (the ileum,

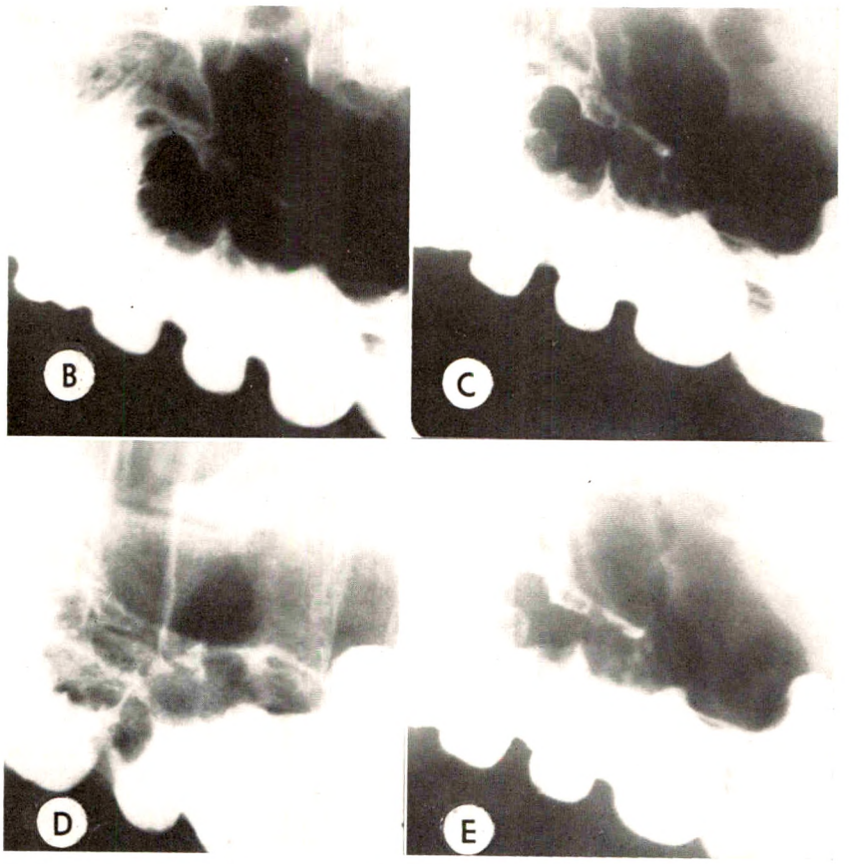


Fig. 2. (*B–E*) Roentgenograms showing the deformity of the hepatic flexure of the colon created by a pericolic abscess.

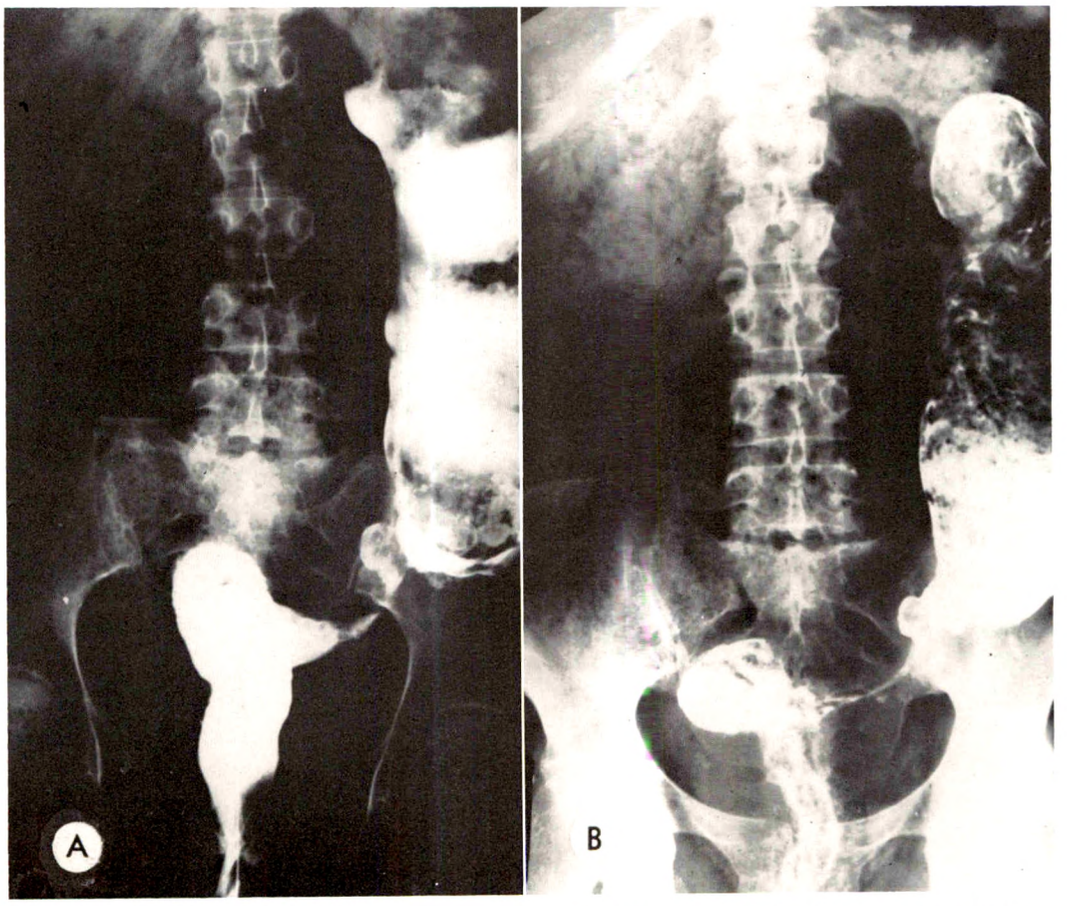


FIG. 3. (*A* and *B*) Roentgenograms showing a stricture of the sigmoid colon in a woman with long standing ulcerative colitis which had healed and produced a megacolon type of deformity.

the stomach, and other viscera) usually demand surgical treatment.

Polyps, pseudopolyps, or mucosal tags commonly follow when the chronic ulcerative colitis is severe and destructive. Extensive mucosal denudation occurs, and the remaining islets of mucosa frequently are considered to be polyps. They are not polyps in the true sense, but are inflammatory mucosal tags with mucus inspissation. Sometimes, they are enlarged by the pulling and tugging of passing feces. These tags should be observed; not infrequently, they shrink with the healing of the colitis. Sometimes they become unrecognizable. As the colitis heals, the mucosal tags in the rectum probably should be removed by fulguration (Fig. 4, *A* and *B*). If any mucosal tags become larger, as they occasionally do, then colectomy should be considered; or a single mucosal tag (pseudopolyp) may be removed. Occasionally, neoplastic changes occur in the head of such a tag, but never in the stalk. Such a lesion is of a low grade malignancy (adenocarcinoma, Grade 1) in an adenoma (Fig. 5).

Massive hemorrhaging, when the patient literally passes bedpans full of blood, occurs rather rarely, and the bleeding usually can be controlled medically. However, a patient may bleed so profusely that transfusion will not replenish the blood supply and a colectomy may become advisable. Roentgenologic examinations employing the barium enema should be performed with care.

Toxic dilatation of the colon (sometimes called toxic megacolon, but better described as macrocolon or toxic distention of

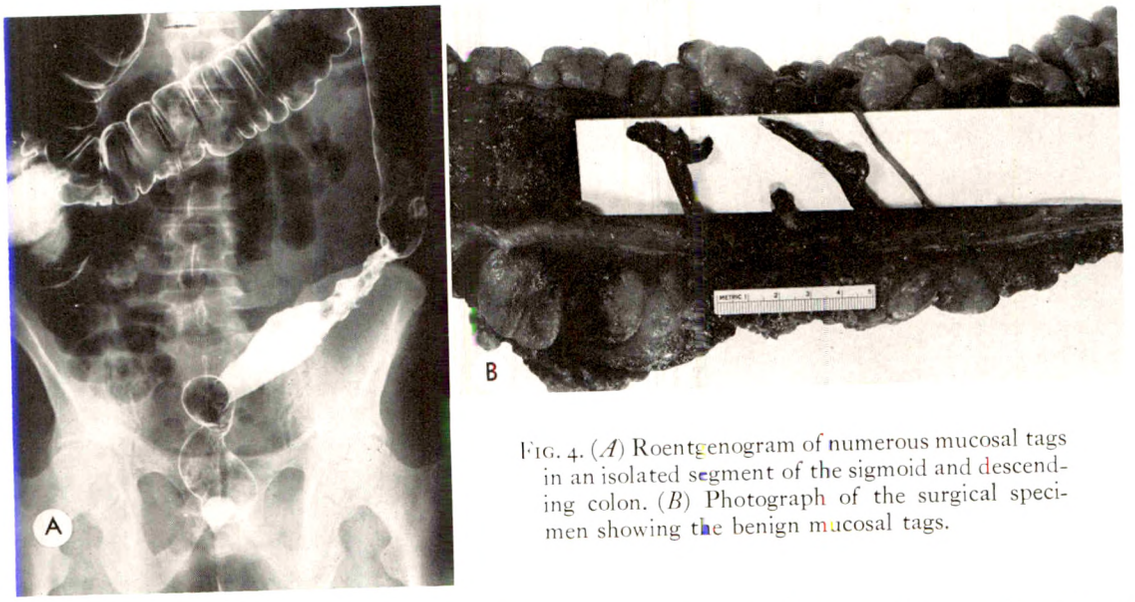


Fig. 4. (*A*) Roentgenogram of numerous mucosal tags in an isolated segment of the sigmoid and descending colon. (*B*) Photograph of the surgical specimen showing the benign mucosal tags.

the colon) presents serious problems (Fig. 6). This toxic distention of the colon may be produced by severe disruption of the muscular coats of the bowel; a disturbance of the myenteric plexus; or, perhaps, the hypokalemia which so frequently occurs. Interestingly, patients usually have received narcotics for days prior to the development of this phenomenon. In most instances, the patient is so sick that surgical



Fig. 5. Roentgenogram demonstrating a single mucosal tag with low grade neoplastic changes at the tip. (Note superimposed surgical specimen.)

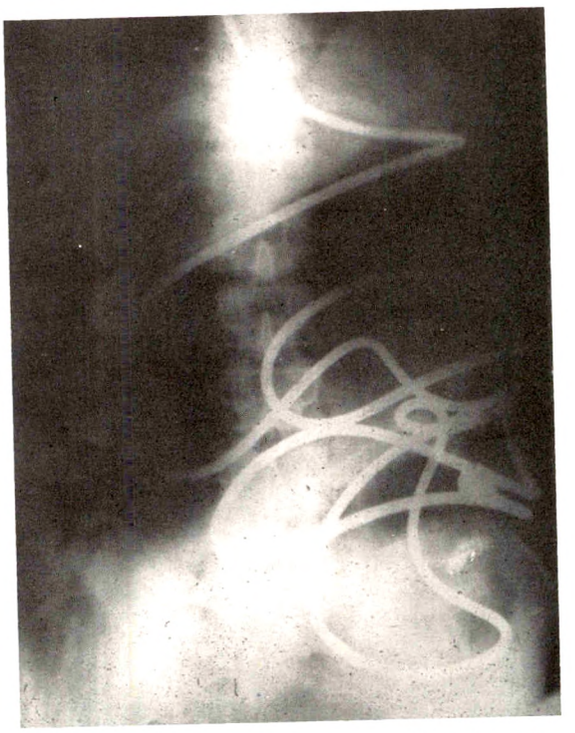


Fig. 6. Roentgenogram of the huge distended colon which is typical of toxic dilatation of the colon. The first case was described in 1950.

intervention at the time of distention carries a grave risk. Intravenous fluids, correction of the electrolytic imbalance, transfusions, and profuse broad spectrum antibiotic therapy usually serve to control the condition. In some instances, however, this is not the case. If the patient is deteriorating, operative therapy probably is indicated. At this stage of the disease, colectomy is perilous.

In ulcerative colitis, perforation of the bowel occurs in two very definite forms. Sometimes, the perforation is a very dramatic event. The cecum may literally "blow out," spilling the intestinal contents into the abdominal cavity. Any operation at this time would be futile. The case of a 2-year-old boy with severe ulcerative colitis involving the entire colon which had perforated numerous times illustrates this serious complication. In another patient, multiple perforations of the transverse colon were observed at the time of barium instillation for roentgenologic examination. The barium flowed into the lesser peritoneal cavity. In a patient with active disease, the barium usually returns to the colon within 24 hours, and not infrequently the acute colitis subsides after this procedure. The risk of instilling barium, of course, is considerable and one hardly dares to consider this procedure as a therapeutic measure. I have never thought that barium instillation was justified at this time, but on several occasions I have inadvertently administered barium to this type of patient. The result was that the colitis became quiescent after the barium receded into the colon. Nevertheless, the colon which allows such a perforation is in a serious state and must be handled extremely gently. When perforation is localized (*i.e.*, in the sigmoid) and a walled-off abscess results, surgical intervention is recommended.

GROUP 3. CONDITIONS WHICH PRESENT PRIMARY SURGICAL PROBLEMS

When fistulas are intra-abdominal and connect viscus to viscus, surgical intervention is the only advisable treatment. Likewise, strictures above the rectosigmoid, (except in the rare instance when one can be certain that they are definitely inflammatory) are surgical problems. Walled-off perforations in the large intestine require operative therapy. When carefully observed pseudopolyps or mucosal tags seem to have increased in size, colectomy should be considered seriously. Toxic dilatation occasionally requires operative intervention.

The most dramatic and most definite indication for immediate operation is for carcinoma which is secondary to ulcerative colitis. This carcinoma occurs in three forms. Small, isolated, single or multiple carcinomatous lesions may develop. These are of the nature of low grade adenocarcinoma in an adenoma. On two occasions, I have seen these neoplasms develop in mucosal tags which have been observed for long periods of time. Even these lesions demand surgical removal. The second form is the well defined localized carcinoma which occurs as a single lesion, or as multiple involvement. If diagnosed early, colectomy will provide a satisfactory result. I recall a woman patient who had 4 malignant lesions (adenocarcinomas, Grades 2 and 3): 1 in the rectum; 1 in the descending colon; 1 in the transverse colon; and 1 at the hepatic flexure. A colectomy was performed, and an ileostomy was established. She consulted me 25 years later for a pelvic problem. Her colitis had been relieved. The third rather unusual form concerns secondary carcinomatosis of the colon. These patients present serious problems and have created the attitude that nothing can be done when carcinoma complicates ulcerative colitis. The carcinoma diffusely fills the colonic wall, innumerable islands of fossae of high grade carcinoma developing simultaneously so that the entire colonic wall becomes a thick tube infiltrated with cancer (Fig. 7, *A* and *B*). Treatment has been totally unsatisfactory.

At the Mayo Clinic in early 1960, I reviewed the clinical records of all patients

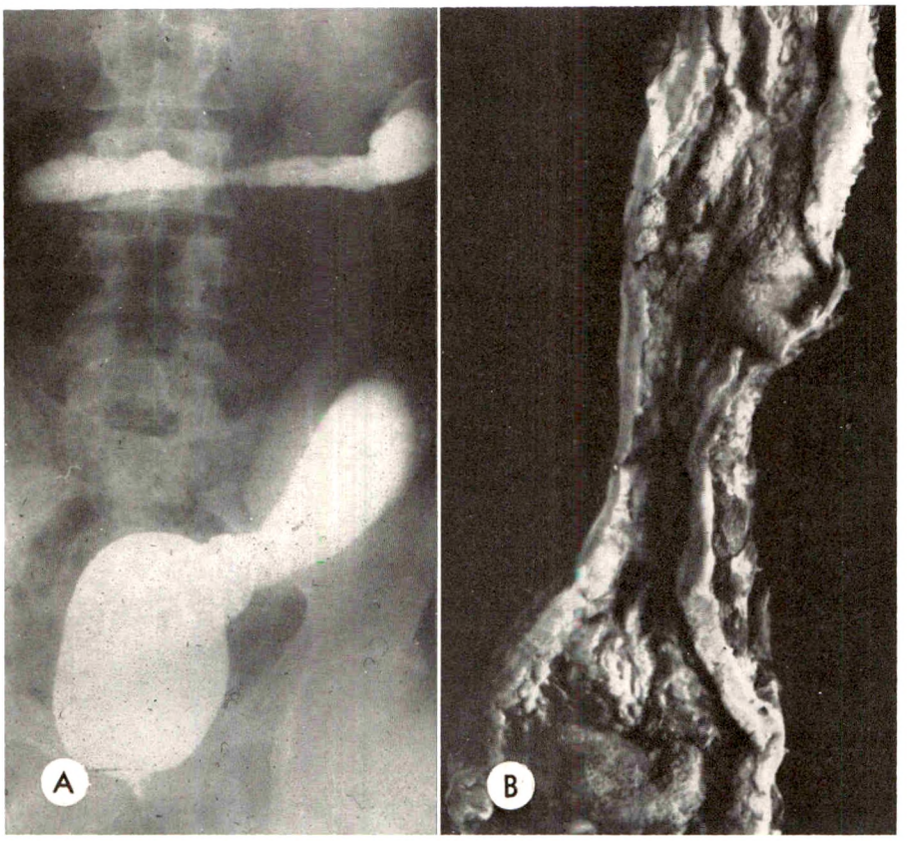


Fig. 7. (*A*) Roentgenogram and (*B*) surgical specimen demonstrating diffuse carcinomatous infiltration.

with ulcerative colitis who developed carcinoma.[2] Whereas 7,000 patients with ulcerative colitis were observed, only 178 of those who subsequently returned to the Mayo Clinic developed carcinoma.* These 178 instances indicated that the carcinoma was inclined to develop some 15 to 18 years after the onset of the ulcerative colitis. Only 27 patients had the diffuse form of carcinomatosis. Others had high grade, single or multiple neoplasms. Surgical exploration seemed advisable in 101 instances; and following surgical resection, 48 per cent were well and alive 5 years later. Although this review indicated that the prognosis for patients with chronic ulcerative colitis and secondary carcinoma is far from hopeless, malignant invasion does present some serious secondary complications. The radiologist can be of great help in diagnosing these carcinomas (Fig. 8, *A* and *B*).

When chronic ulcerative colitis begins during the first decade of life (particularly before a child is 5 years of age), the disease is apt to deplete the child so much that he fails to grow, fails to develop secondary sexual characteristics, and becomes a small undeveloped person. Frequently, this underdevelopment is mistaken for pituitary infantilism. This pseudoinfantilism may be controlled if the colitis is treated vigorously and the condition is controlled before the child reaches puberty. However, when the colitis is not controlled and growth does not occur, colectomy may produce a result similar to that possible through vigorous medical treatment. Ileostomy and colectomy have been successful procedures in some of these patients.

* Patients with small low grade adenocarcinomas and adenomas were not included, and many may have developed carcinoma which was diagnosed elsewhere.

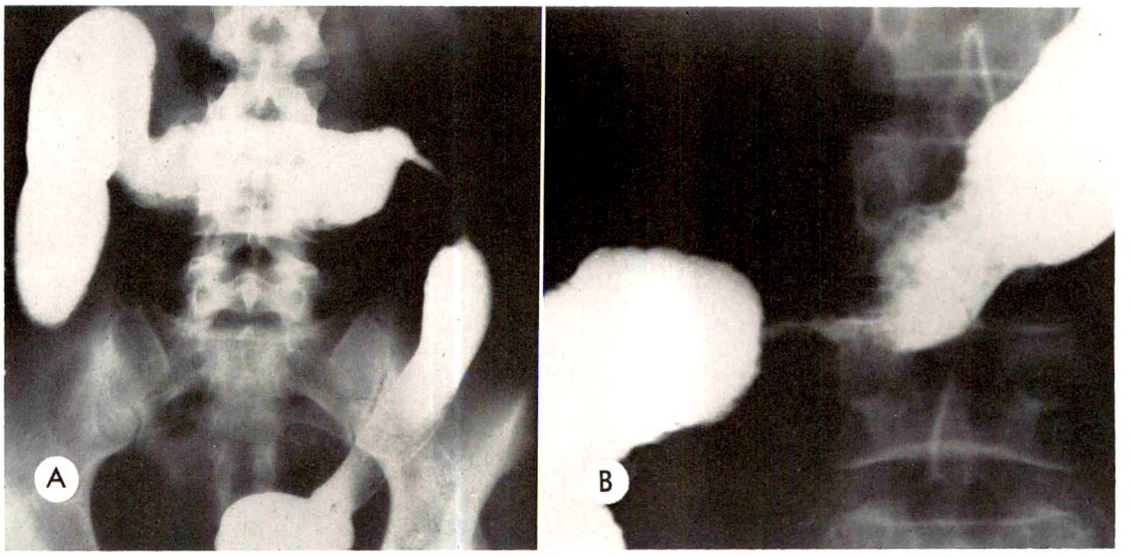


FIG. 8. (*A*) Roentgenogram of a typical colonic deformity produced by carcinoma secondary to advanced ulcerative colitis. (*B*) An atypical deformity produced by carcinoma in a colon which was the seat of advanced ulcerative colitis.

COMMENTS

Many serious complications or sequelae may be associated with chronic ulcerative colitis, and a patient's prognosis depends largely on avoiding or controlling these complications. Because the radiologist is the key figure in the diagnostic team, for him to make a diagnosis of chronic ulcerative colitis hardly seems sufficient. He can do much more by describing the nature, activity, and severity of the colitis, the amount of damage to the bowel and its wall, and whether or not he considers that the disease is of the granulomatous or the simple ulcerative type.[3] He can help in appraising the unpleasant sequelae which frequently are associated with the ulcerative colitis, and in ascertaining the nature of lesions which appear to be polyps in the colon, the seat of the ulcerative colitis. When describing the mucosal changes during active disease in a patient who has severe mucosal denudation, it is unwise to speak of polypoid degeneration. It is unwise to speak of polyps when the condition heals and mucosal tags remain; these should be called pseudopolyps. The radiologist can assist in the evaluation of toxic dilatation of the colon, mistakenly called toxic megacolon. He can help to determine the nature of obstructing lesions—whether strictures are inflammatory or neoplastic. Of course, acute judgement is required, but an experienced radiologist usually can distinguish between inflammatory post-ulcerative colitis strictures and secondary neoplasms.

A roentgenologic examination of the colon must be performed with care when perforation is suspected. In these patients, the bowel wall has been described as being as brittle as "blotting paper." Superfluous manipulation may force the barium through the interstices of the bowel wall itself. This has happened rarely, and fortunately, the barium has returned to the lumen of the bowel. The performance of such a maneuver in itself, however, seems rather dangerous. The roentgenologist can be particularly helpful in locating and isolating fistulas between neighboring viscera, *i.e.*, between the colon and ileum and the colon and stomach.

SUMMARY

This presentation summarizes my lifelong experience with patients whose colons

have been the seats of a rather virulent and damaging disease, chronic ulcerative colitis. The complications and sequelae which may afflict these unfortunate persons have been emphasized, and I have offered hints concerning their diagnosis and management.

The care of each patient with chronic ulcerative colitis requires patience, perseverance, and a well organized therapeutic program from which he is not allowed to stray. The physician must be on the alert for the development of complications, and when they occur he must treat them as secondary problems, while attacking the disease in the colon more vigorously. Then, with close cooperation of the patients, the disease can be controlled in more than 75 per cent of those suffering from this so-called intractable disorder.

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ANGIOGRAPHY IN ULCERATIVE COLITIS*

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FOR many years sigmoidoscopy and roentgen examination of the colon using barium enema have been the only methods available for diagnosing and following the course of ulcerative colitis. Double contrast roentgenography has improved the diagnosis of the early lesions of the mucosa, but there are still discrepancies between the results of such an examination and sigmoidoscopy.

Advances in selective angiography have made it possible to study the appearance of the vessels supplying the colon. Useful visualization now includes not only the large central branches but also the delicate vasa recta and their branches in the wall of the bowel. A number of patients with the diagnosis of ulcerative colitis was selected for the purpose of discovering whether changes of these vessels were discernible.

MATERIAL AND METHOD

The material consists of 10 patients, aged 14 to 45 years, with a diagnosis of ulcerative colitis established by proctoscopy and roentgen examination of the colon. The patients had had the disease from 3 weeks to 20 years. Colectomy was performed later on 4 of the patients. In all 10 patients the inferior mesenteric artery was catheterized and in 4 of them the superior mesenteric artery also.

The vascular supply of the normal colon was studied in 3 patients, aged 18, 35 and 66 years. In these patients selective arteriography of the inferior mesenteric artery was performed in association with selective renal angiography.

The examinations were done with retrograde catheterization via one of the femoral arteries with the use of Ödman-Ledin radiopaque catheter (Kifa, Sweden). The outer diameter of the catheter was 2.2 mm. and the inner diameter 1.2 mm. The tip was shaped according to Ström and Winberg.[12] Just before the injection of the contrast medium, the colon was insufflated with air to facilitate examination of its intramural vessels. With a Gidlund automatic injector 15 ml. of urografin 76 per cent (Schering) was injected at a rate of about 8 ml./sec., after which 2 angiograms were taken per second for 4 seconds and then 1 every other second for 14 seconds.

RESULTS

The angiographic appearances in the 3 controls were largely the same. The diameter of the inferior mesenteric artery just beyond its origin from aorta was 4 mm. in all 3 cases. The vasa recta arising from the marginal artery and sigmoid arteries were very delicate. They tapered off towards the periphery of the intestine where they were so narrow they were barely discernible. The veins in the intestinal wall were narrow and filled with contrast medium in low concentration. The contrast medium appeared in them 8, 10 and 12 seconds after the beginning of the injection of the contrast medium.

Two patients with ulcerative colitis were symptom free at the time of the angiographic examination and study of the colon with barium did not reveal any abnormality. The inferior mesenteric artery was catheterized in both of these patients, along with the superior mesenteric artery in one. The diameter of the inferior mesenteric artery was 4 mm. and 5 mm., respectively. The vasa recta were delicate and, as in the controls, tapered off towards the periphery. In 1 case the contrast medium appeared in the narrow veins in the intestinal wall 12 seconds after the injection, while in the other the concentration of the contrast

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medium in the veins was too low to allow examination of these vessels.

In the remaining 8 cases, previous proctoscopy and roentgen examination of the colon with barium and air contrast had shown mucosal changes (Fig. 1*A* and 2*A*). In 5 patients angiography was done with catheterization of the inferior mesenteric artery only. In the remaining cases, both the superior and the inferior mesenteric arteries were catheterized. In 1 case the diameter of the inferior mesenteric artery could not be measured because of spasm. In the remaining cases, the diameter was increased and varied between 4.5 mm. and 6.5 mm. (mean 5.4 mm.) The middle colic, right colic and ileocolic arteries from the superior mesenteric artery were widened also. All the cases showed wide vasa recta extending from the marginal artery and the sigmoid arteries. The most striking observation was that most of these vasa recta did not taper off towards the periphery as they did in the controls (Fig. 1 *B* and 2 *B*). In some cases the vasa recta terminated abruptly as if they were occluded, and the periphery of the intestine was supplied only by very narrow, irregularly distributed, arteries (Fig. 1 *B*). In the capillary phase, a moderate increase in thickness of the bowel wall was noted. The veins in the intestinal wall were markedly dilated and their course irregular. They usually filled quite rapidly with contrast medium in high concentration. Vein filling occurred 2.5 to 8 seconds (mean 4.1 sec.) after the injection (Fig. 1 *C* and 2 *C*). The larger veins were abnormally wide and the contrast filling unusually dense.

DISCUSSION

Microscopic examination of the intestine has shown that the peripheral vessels in the wall of the colon are involved in ulcerative colitis.[13] In severe cases of the disease, these authors found an inflammatory necrosis of the blood vessels and they believed this to be a cause of the ulcerations in the mucosa. In some respects, the vascular lesions resembled those in periarteritis nodosa, thromboangiitis obliterans and related diseases.

It is difficult to decide whether the affection of the vessels is primary or secondary to the inflammatory changes in the intestinal mucosa. Certain factors suggest that the vascular changes are the primary ones. Mucosal lesions of the type occurring in ulcerative colitis with edema, ulcerations and pseudopolypoid formations have also been seen in patients after shock.[4,8] Mes-

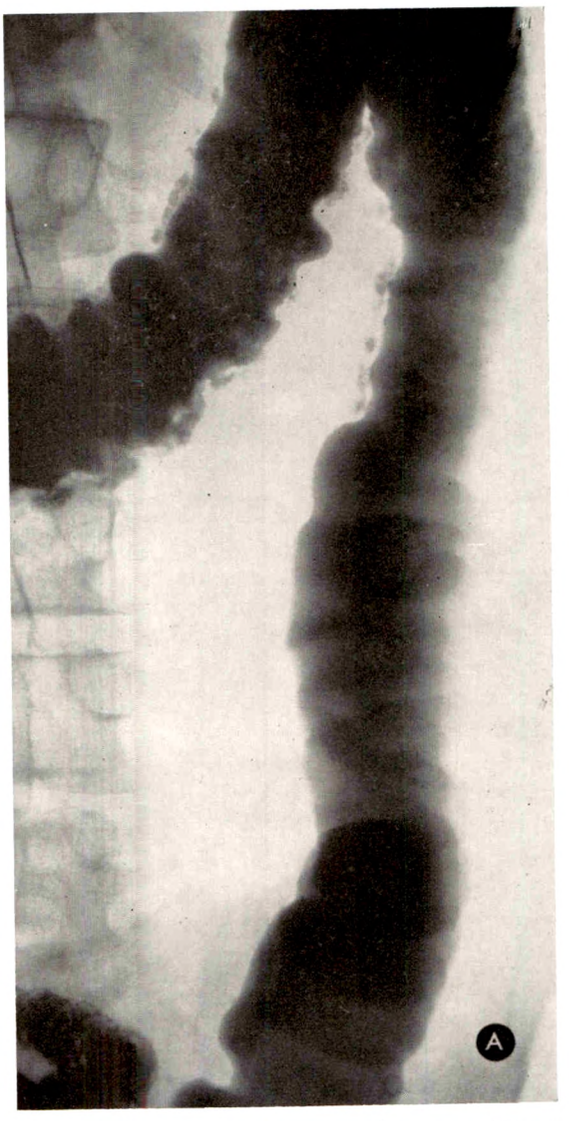


Fig. 1. O.E., a 45 year old male with a 3 year history of ulcerative colitis. (*A*) Barium enema examination shows edematous wall of the colon with marked pseudopolyposis.

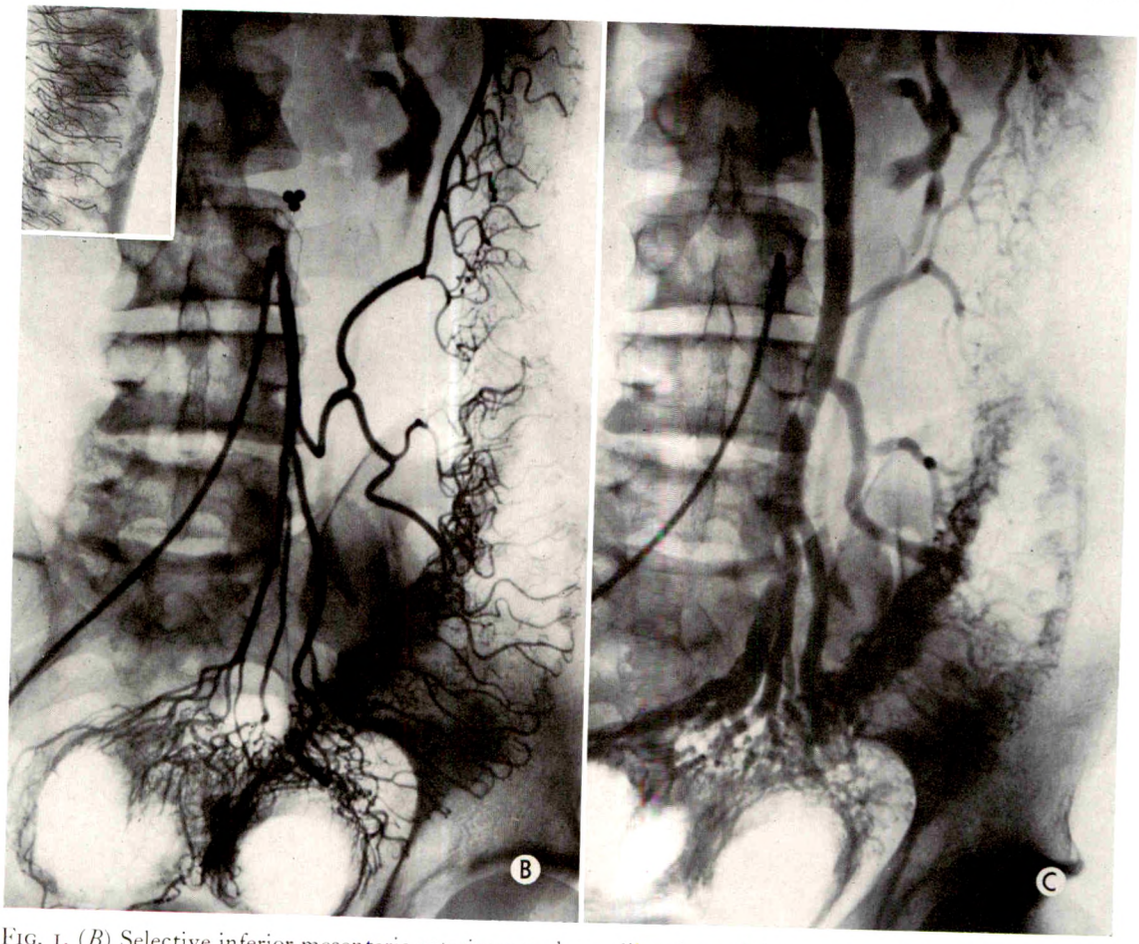


FIG. 1. (*B*) Selective inferior mesenteric arteriogram shows dilated supplying arteries of the colon. Note the wide vasa recta in the bowel wall. *Insert.* Surgical specimen of the descending colon injected with barium. The vasa recta are occluded in the periphery which is supplied by narrow newly-formed vessels. (*C*) Venous phase. Dilated veins with high concentration of contrast medium.

enteric vascular insufficiency was believed to be a probable cause of the changes. This is supported by investigations on laboratory animals by Corday *et al.*,[4] who induced shock in dogs, with resultant mucosal changes and blood stained diarrhea.

In recent years, cases have been reported in which barium contrast examination of the colon, because of blood-stained stools, showed changes resembling those seen in ulcerative or granulomatous colitis. Subsequent operation or sigmoidoscopy showed that the lesions were due to submucous hemorrhages from infarction with secondary mucosal ulceration and edema.[2,4,5,10] Angiographic examination or dissection of the blood vessels often failed to demonstrate occlusive vascular changes. Here, too, vascular spasm was thought to be the cause of the changes in the intestinal mucosa. Vasospasm may also be the cause of segmental ulcerations and stenosis sometimes occurring after oral potassium therapy.[1,3,7,8] Pseudopolypoid mucosal changes and ulcerations sometimes have a clear vascular origin which is shown clinically,[5] as well as in laboratory animals.[2,10]

Preoperative arteriographic examinations of patients with ulcerative colitis have been reported only by Ödman,[9] who on angiography of the superior mesenteric artery pointed out that the vascular ar-

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cades in the colon were irregular and wide and that the veins filled unusually early. Ström and Winberg,[12] who studied the angiographic appearance of cancer of the colon reported that early filling of draining veins was not obtained in cases with inflammatory lesions. In adenocarcinoma of the colon, however, they were able to demonstrate rapid contrast filling of the veins from the pathologically changed part of the bowel.

In ulcerative colitis we have found the arteries supplying the diseased bowel to be widened but to show no lumen irregularities. The vasa recta in the wall of the colon were unusually wide and did not taper off towards the periphery in the same way as was seen in the controls. This might be of differential diagnostic value in distinguishing the disease from granulomatous colitis, where the peripheral arteries in the intestinal wall appear to be abnormally narrow, tortuous and with irregular lumen (Fig. 3).

In ulcerative colitis the filling of the veins occurred much earlier and the concentration of the contrast medium within them was much higher than in the controls. The veins in the intestinal wall appeared varicose and tortuous. Because of their width and high concentration of the contrast medium, they were readily distinguished, while in the controls these veins were delicate and the concentration of their filling was so low that they could barely be identified.

Most likely, these vascular changes in the colon are due to an increased flow of blood during the inflammatory stage and thus secondary to the colitis. Arteriovenous shunting was observed by Lagergren *et al.*[6] at angiography in some cases of chronic inflammation. They explained this arteriovenous shunting by an abundance of capillary vessels in the granulation tissue. Observations by Ström and Winberg[12] in arteriographic examination of diverticulitis with peridiverticulitis argue against the inflammatory condition as the only cause of the rapid passage of the contrast medium from the arteries to the veins. The possibility of a vascular genesis of the ulcerative colitis is to be considered.

Spanner[11] described the occurrence of arteriovenous shunts in the submucosa and mucosa in both experimental animals and in men. Endocrine or metabolic disorders



Fig. 2. L.J., a 23 year old male with a 2 year history of ulcerative colitis. (*A*) Air contrast study of the descending colon shows ulcerations and pseudopolyposis.

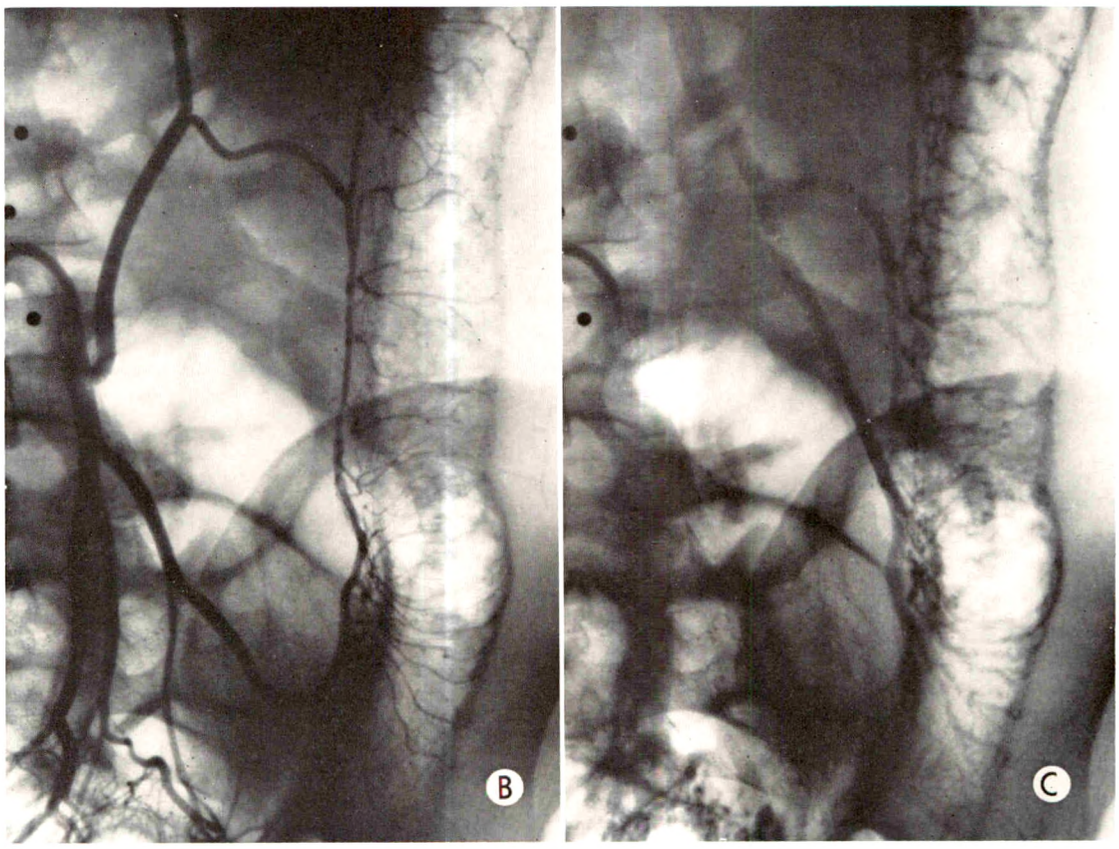


FIG. 2. (*B*) Selective inferior mesenteric arteriogram. The proximal branches are wide but the vasa recta in the bowel wall are only slightly dilated. (*C*) Venous phase shows marked dilatation of the veins in the bowel wall. The concentration of the contrast medium is high in all draining veins.

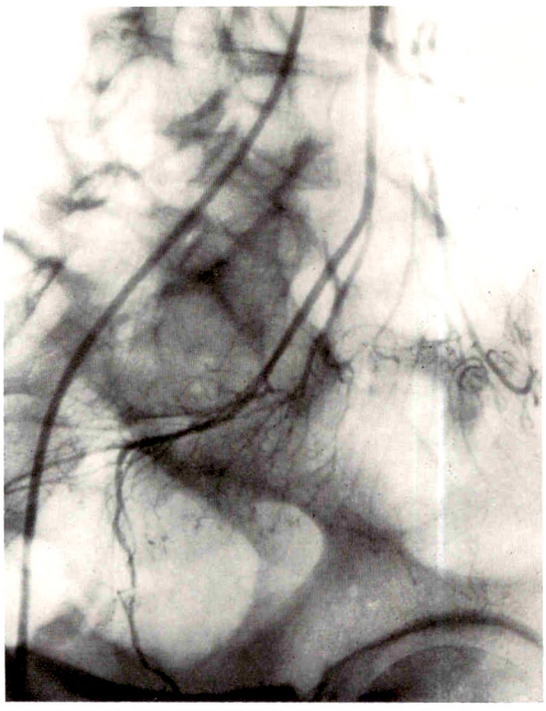


FIG. 3. Selective inferior mesenteric arteriogram of a 43 year old male with stenosing granulomatous colitis of the sigmoid. Normal wide supplying arteries. Tortuous vasa recta.

or allergic manifestations may influence these shunts so that the blood does not reach the mucosal capillaries. This might produce ischemia, which, when severe, can cause necrosis, edema and ulceration. Our knowledge of the pharmacodynamic control of these shunts is, however, not sufficient to warrant any conclusions about

their etiologic importance in the causation of ulcerative colitis.

SUMMARY

Selective inferior mesenteric angiography was carried out on 10 patients with the clinical diagnosis of ulcerative colitis. Four of these patients were also examined with catheterization of the superior mesenteric artery. The angiographic findings are discussed as well as the possible vascular origin of ulcerative colitis.

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SEGMENTAL ULCERATIVE COLITIS VERSUS SEGMENTAL CROHN'S DISEASE OF THE COLON*

A ROENTGENOGRAPHIC AND PATHOLOGIC STUDY

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ROCHESTER, MINNESOTA

ULCERATIVE colitis had been recognized for some time when Bargen and Weber,[1] in 1930, reported 23 cases in which the rectal mucosa was spared, in contrast to the usual picture in which the rectum bore the brunt of the disease. In 1932, Crohn and co-workers[3] described what is now known as regional enteritis. Grossly, it was characterized by mucosal ulceration, multiple fistulas, and, sometimes, thickening and stenosis of the terminal ileum; microscopically, there was a granulomatous inflammatory process, often with giant cell systems. It involved all coats of the small intestine. The authors stated that this process did not involve the colon; however, subsequent studies[9,13] have amply confirmed the fact that regional enteritis does affect the right colon in about 30 per cent of cases.

Neuman and Dockerty[11] described the pathologic findings in segmental ulcerative colitis, and Warren and Sommers[12] described the changes in Crohn's disease. Marshak and associates[6–8,14,15] discussed the roentgenologic features of Crohn's disease of the colon, a process they termed "granulomatous colitis."

In general, ulcerative colitis has been considered to be a colonic lesion, and regional enteritis has been considered to be a disorder of the small intestine. Major involvement of both organs has been described by a multitude of terms, including some which expressed uncertainty regarding the relationship to "ordinary" ulcerative colitis, on the one hand, and "ordinary" regional enteritis, on the other. Recently, attention has been focused on certain cases of colitis in which the pathologic picture resembled that of regional enteritis or Crohn's disease. The present study was carried out to determine whether these cases, which are tentatively classified as Crohn's disease of the colon, can be distinguished from cases of ordinary ulcerative colitis by means of roentgenography after a barium enema.

MATERIALS AND METHODS

In this study, to determine if ulcerative colitis and Crohn's disease of the colon (Crohn's colitis) could be distinguished roentgenographically, it was necessary to use cases with histopathologic verification. About 300 resections had been performed at the Mayo Clinic from 1954 through 1964 for ulcerative colitis or other forms of idiopathic colitis (sometimes affecting the small intestine as well). In approximately 50 of these cases, the pathologic report suggested that the process did not involve the entire colon. From these 50 cases, those without roentgenograms and preserved tissue, those in which previous bowel resections had been done elsewhere, and those in which carcinoma had developed were rejected, leaving a total of 17 cases for this study. Nine were idiopathic segmental colitis without involvement of the ileum, and 8 were retional enteritis with a major portion of the colon involved as well. For comparison, 8 cases of diffuse chronic ulcerative colitis, all with "backwash ileitis," were selected at random as a control group so that the changes in the ileum could be compared

* Mayo Clinic and Mayo Foundation: Section of Roentgenology (Dr. Carlson) and of Surgical Pathology (Dr. Dockerty). Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Radiology (Dr. Reeves).

with the changes seen in regional enteritis.

The roentgenographic and pathologic features of all cases were analyzed. Surgical specimens preserved in 10 per cent formalin were studied, with special attention to thickness of the intestinal wall and "skipped" areas of normal mucosa between diseased areas. Sections were made from margins of the lesions and from areas of severe involvement. This tissue was "rejuvenated" so that fresh hematoxylin and eosin slides could be prepared and used to designate each case as either ulcerative colitis or Crohn's colitis.

Roentgenograms made after barium enema administration and, sometimes, during examination of the small intestine were studied. First, the report of the examining radiologist was compared with the pathologic findings in order to determine the accuracy of the roentgenographic examination in discovering the lesions and in predicting the type. Then, the roentgenograms were studied retrospectively, with a search for strictures, pseudopolyps, deep ulcers, sinuses, and fistulas, features which might be helpful in differentiating Crohn's colitis from ulcerative colitis.

RESULTS

Pathologic Features. In 7 cases of segmental ulcerative colitis and 7 cases of diffuse chronic ulcerative colitis (control group), the predominant microscopic appearance was ulceration with inflammation limited almost exclusively to the mucosa and submucosa (Fig. 1, *left*). Crypt abscess was a frequent finding at the margin of the lesions (Fig. 1, *right*). Hyperganglionosis was also frequently noted. The gross appearance was variable, depending on the length of intestine involved, but the thickness of the wall was either normal or slightly increased at most. Shortening of

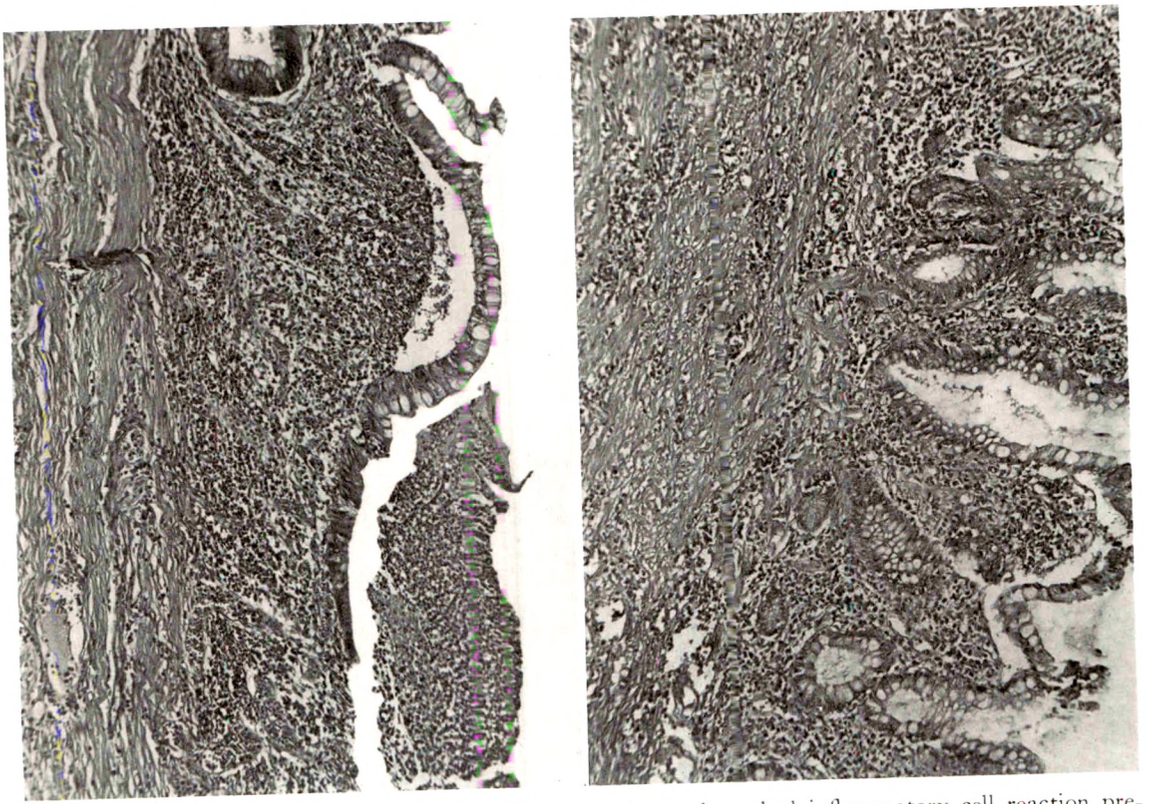


Fig. 1. Chronic ulcerative colitis. *Left:* Mucosal ulceration and marked inflammatory cell reaction predominantly affecting the mucosal and submucosal layers. (Hematoxylin and eosin; ×100.) *Right:* Submucosal inflammation with crypt abscesses. (Hematoxylin and eosin; ×100.)



FIG. 2. Segmental ulcerative colitis involving ascending colon, transverse colon, and splenic flexure, in 38 year old woman who had had recurrent melena for 5 years.

the intestine, stiffening of its wall, and pseudopolyps were constant features (Fig. 2). When the process extended into the ileum, the appearance grossly and microscopically was similar to that in the colon—namely mucosal and submucosal inflammation with ulceration and little or no mural thickening.

In 2 cases of Crohn's colitis and 8 cases of Crohn's colitis with regional enteritis, the microscopic appearance was minor ulceration with fairly marked inflammation of all coats of the intestinal wall, including the muscle and serosa (Fig. 3, *left*). Although somewhat scattered, histiocytes and giant cell granulomas (Fig. 3, *right*) were seen in all but 1 case. Grossly, this involvement of all layers of the wall resulted in a significant

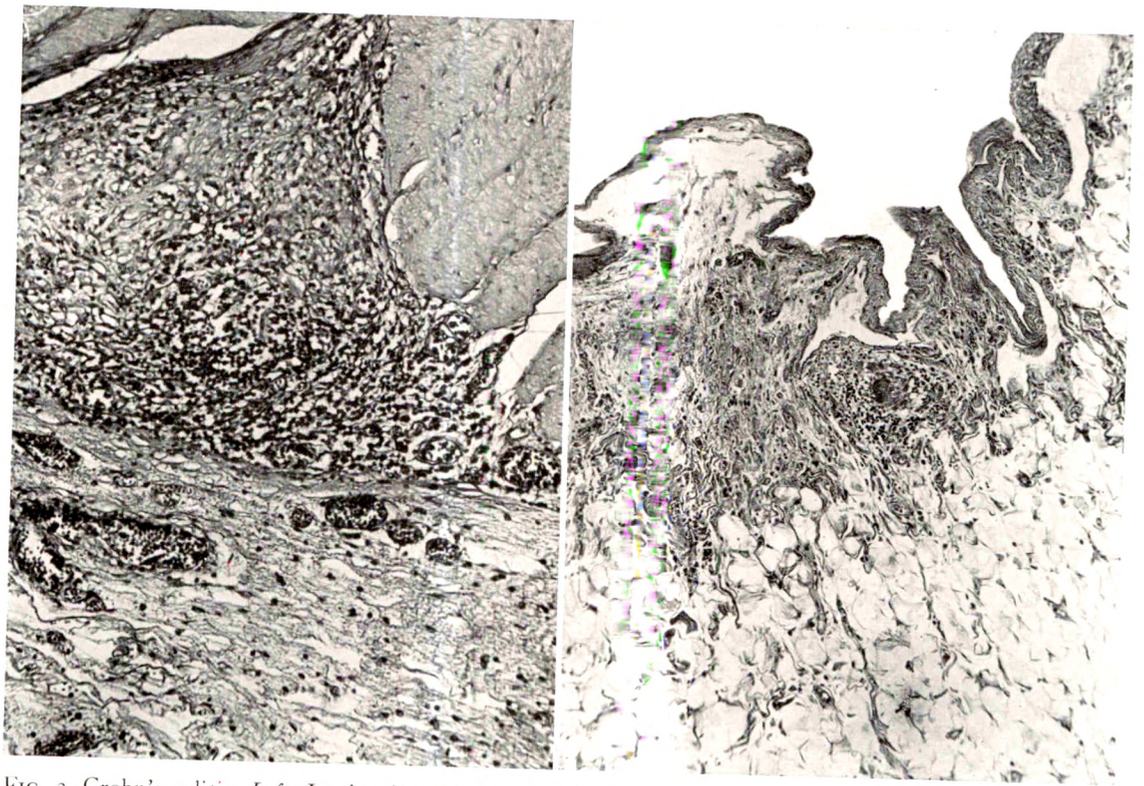


FIG. 3. Crohn's colitis. *Left:* In the sigmoid, associated with regional enteritis causing inflammation of all layers with marked thickening of the bowel wall. Note greatly thickened submucosal layer and a small portion of a thickened muscularis layer. (Hematoxylin and eosin; ×150.) *Right:* In the ascending colon, associated with regional enteritis. Note characteristic giant cell granuloma in the subserosal layer. (Hematoxylin and eosin; ×100.)

thickening which was quite distinctive (Fig. 4). In some regions this proliferation caused pronounced narrowing of the lumen, leading to stricture. Again, hyperganglionosis was noted. In the ileum involved with regional enteritis, the picture was similar, with thickened wall, stenotic lumen, and, microscopically, scattered granulomas with giant cells. The cases of combined Crohn's colitis and regional enteritis had three distinct patterns of location in the colon (Table I): 3 lesions extended across the ileocecal valve to involve the ascending colon, 3 involved only the sigmoid, and 2 exhibited alternating normal and diseased areas in skip fashion through the ascending, transverse, and upper descending colon.

Roentgenographic Features. The original roentgenographic examination was more capable of finding the lesion than of indicating its exact nature. The single instance of failure to detect the inflammatory process in the segmental ulcerative colitis group (Table II) was due to obstruction to the retrograde flow of barium by an abcess related to a lesion involving the descending colon. In the 4 cases of Crohn's colitis with regional enteritis in which the barium enema study revealed no colonic lesion, regional enteritis was diagnosed on either a

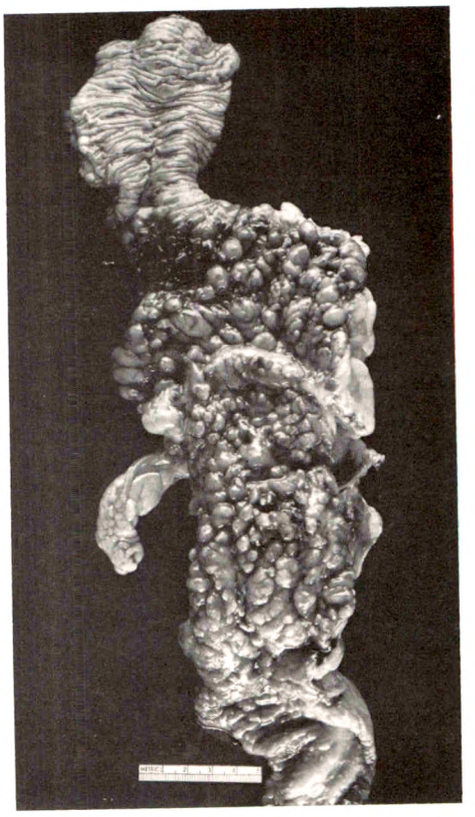


Fig. 4. Regional enteritis with Crohn's colitis involving the ascending colon. Mucosal ulceration, pseudopolyps, and marked thickening of the wall characterized the process in a 12 year old boy. This patient was the youngest in the series and had diarrhea, abdominal cramps, and perirectal abscesses.

Table I

Location of Lesions

Pathologic Diagnosis	Total No.	Location in Colon					
		ascending colon	transverse colon	splenic flexure	descending colon	sigmoid colon	two or more sites
Segmental ulcerative colitis	7	1	1	2	1	0	2
Crohn's colitis	2	0	0	2	0	0	0
Crohn's colitis with regional enteritis	8	3	0	0	0	3	2
Total	17	4	1	4	1	3	4

TABLE II

ORIGINAL ROENTGENOGRAPHIC INTERPRETATION IN 17 CASES OF SEGMENTAL COLITIS

Pathologic Diagnosis	Total No.	Exclude Carcinoma	Localized Colitis	Miscellaneous	Not Seen
Segmental ulcerative colitis	7	4	1	1	1
Crohn's colitis	2	2	0	0	0
Crohn's colitis with regional enteritis	8	1	1	2	4
Total	17	7	2	3	5

colonic roentgenogram or an examination of the small intestine.

That these lesions frequently resemble, or lead the radiologist to suspect, carcinoma is readily apparent from the original impressions. Most of the time, the radiologist recognized that the area was affected by localized colitis and thought that the appearance was suggestive of carcinoma developing in the involved region.

The distribution of those roentgenographic characteristics that might be helpful in differential diagnosis is shown in Table III. The strictures (Fig. 5, *A–D;* and 6) averaged 4 to 5 cm. in length and all but 1 were associated with Crohn's colitis. All but 1 of the obvious pseudopolyps were seen in cases of ulcerative colitis. Deep ulcerations or sinuses have been frequently mentioned as forerunners of the fistulas seen in Crohn's colitis, but these were detectable roentgenographically in only 3 cases, all of ulcerative colitis (Fig. 7). One fistula, between the sigmoid and terminal ileum, was found in this series in a case of Crohn's colitis with regional enteritis (Fig. 8).

In addition there is another change commonly seen in both ulcerative colitis and Crohn's colitis which is hard to describe in words. In the roentgenogram of a region of colitis with shallow ulceration and shortening, there is often an irregular, asymmetric deformity which makes one think of a neoplasm arising in a segment of colitis (Fig. 5, *A, B* and *C;* and 7). This finding was most common in those cases in which the original impression had been that malignant neoplasm might be present. Nine of the 24 cases exhibited this: 5 cases

TABLE III

ROENTGENOGRAPHIC CHARACTERISTICS OF SEGMENTAL COLITIS

Pathologic Diagnosis	Total No.	Stricture	Pseudopolyp	Deep Ulcer	Fistula
Segmental ulcerative colitis	7	1	1	2	0
Crohn's colitis	2	1	1	0	0
Crohn's colitis with regional enteritis	8	3	0	0	1
Diffuse ulcerative colitis with backwash ileitis	7	0	4	1	0
Total	24	5	6	3	1

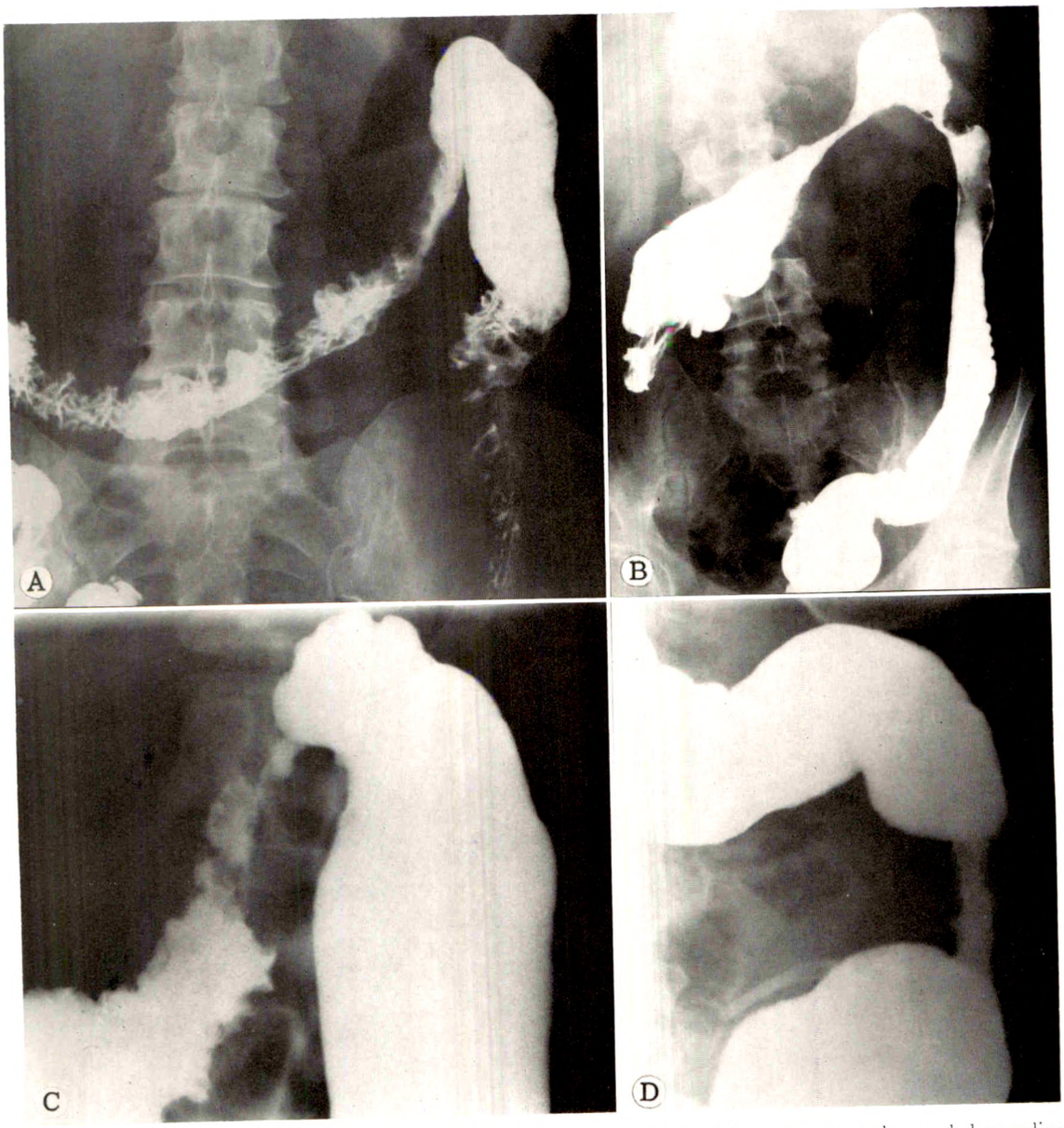


Fig. 5. (*A*) Crohn's colitis causing an irregular deforming area in the left transverse colon and descending colon. The radiologist could not exclude carcinoma. The patient, a 54 year old woman, had experienced intermittent diarrhea and cramps for 15 years. Proctoscopy gave normal results on several occasions. (*B*) Segmental ulcerative colitis with 2 strictures, in the splenic flexure and transverse colon, showing features unusual for ulcerative colitis. The appearance was thought to be compatible with carcinoma by the examining radiologist. The patient, a 54 year old man, reported bloody diarrhea of 1 month's duration. On proctoscopy, the mucosa bled more easily than normal. (*C*) Crohn's colitis of splenic flexure, without small bowel disease. The process narrows the bowel, causing a long stricture. The original interpretation by the radiologist was that carcinoma could not be excluded. The patient, a 50 year old woman, had had abdominal pain for 2 months and had anemia. (*D*) Crohn's colitis with a stricture in the upper descending colon in a 60 year old woman with regional enteritis. The patient had had diarrhea for 5 years. Proctoscopic findings were normal.

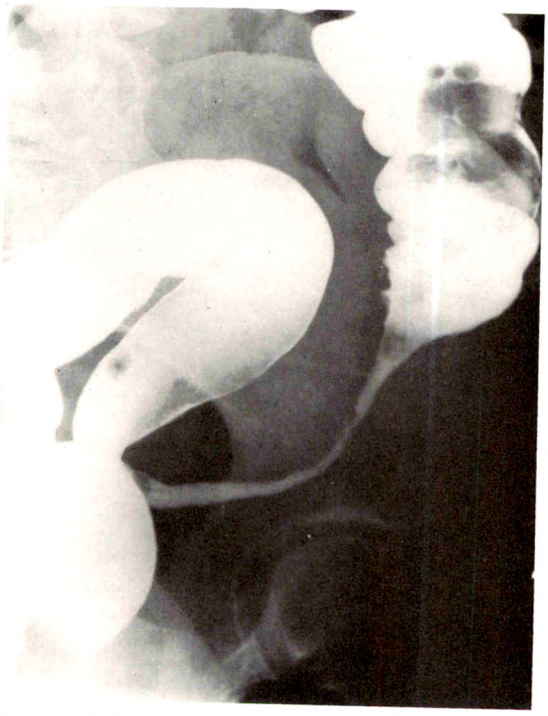


FIG. 6. Crohn's colitis with a long stricture in the sigmoid secondary to regional enteritis in a 44 year old woman. Resection of the terminal ileum, for regional enteritis with a pelvic abscess, had been done some 3 years before this examination. Proctoscopic findings were reported as atypical in that the mucosa bled with "minimal trauma."

of segmental ulcerative colitis, 2 cases of diffuse chronic ulcerative colitis, 1 case of Crohn's colitis, and 1 case of Crohn's colitis with regional enteritis.

The various features (Fig. 9) common to all forms of colitis, namely, ulceration, shortening, and loss of haustration were seen retrospectively in all except 3 cases of Crohn's colitis with regional enteritis in which the colon still appeared to be normal. On pathologic examination, the process extended to the hepatic flexure in 2 of these 3 cases and to the middle of the transverse colon in the third. In 2 other cases of Crohn's colitis with regional enteritis in which the colonic lesion was apparent on the roentgenogram after barium enema administration, the lesion was not apparent on small bowel roentgenograms even though the involved colonic segment was somewhat filled with contrast medium.

Clinical Features. Most of the cases of Crohn's colitis and of segmental ulcerative colitis occurred in patients in the third, fourth, and fifth decades of life. The 2 patients with Crohn's colitis with no involvement of the small intestine were 50 and 54 years old, but the patients with Crohn's colitis with regional enteritis were 12 to 60 years old (mean, 27.6 years). Patients with segmental ulcerative colitis were 34 to 63 years old (mean, 45.4 years). There was no sex predominance. All patients were Caucasian except for 1 Negro woman with Crohn's colitis.

Based on the date of the first symptoms, the interval from onset to operation was highly variable, ranging from 2 months to 20 years. Diarrhea was a complaint in all but 4 of the cases. Although several of the patients in both groups occasionally had bloody stools with their diarrhea, the amount of blood was usually not impres-



FIG. 7. Segmental ulcerative colitis of the left transverse and descending colon. Note 2 deep sinuses just beneath the splenic flexure; there was enough deformity in this area to make the examiner suspicious of carcinoma. The patient, a 34 year old woman, complained of diarrhea and abdominal pain which had been present 1 year. Results of proctoscopy were normal.



Fig. 8. Crohn's colitis with regional enteritis, showing a short stricture in the sigmoid with a fistula from this point to the terminal ileum. The patient, a 20 year old woman, had noted left lower quadrant pain without diarrhea for 1 year. Proctoscopic findings were normal.

sive. However, 2 patients with segmental ulcerative colitis had significant bleeding; 1 had intermittent melena for 5 years and the other had bleeding, severe enough to require transfusions, for 4 months. Also, 1 patient with Crohn's colitis had anemia of unknown origin but had no recollection of melena or rectal bleeding. Abdominal cramps were a frequent complaint in both groups. Perirectal complications, such as anal fistulas and abscesses, occurred in 3 of the 7 patients with segmental ulcerative colitis and in 6 of the 8 patients who had Crohn's colitis with regional enteritis.

Proctoscopic examination was performed in all but 1 case. Except for evidence of perirectal disease, the mucosa was normal in all but 3 cases:* in 2 of these, the mucosa was said to bleed more easily than normal and in 1, a case of long-standing segmental ulcerative colitis, there was slight mucosal thickening.

* Some investigators[2] emphasize that the perianal disease associated with Crohn's colitis is frequently a granulomatous inflammatory process—Crohn's proctitis.

The surgical treatment for all these cases was similar: resection of the diseased region with end-to-end anastomosis. The results (Table IV) of operation were determined either by follow-up examinations at this clinic or through inquiry by questionnaire.

DISCUSSION

Pathologic Features. Important in the study of idiopathic colitis is clear definition of the nomenclature and classification of the various possible disease conditions. Throughout this study, the terms "ulcerative colitis" and "Crohn's disease of the colon" or "Crohn's colitis" have been used to describe the two pathologic states. It is important to note that the term "segmental colitis" is nonspecific with respect to pathologic type, and that either "ulcerative" or "Crohn's" must be added in order to adequately define it.

The differential features found in these

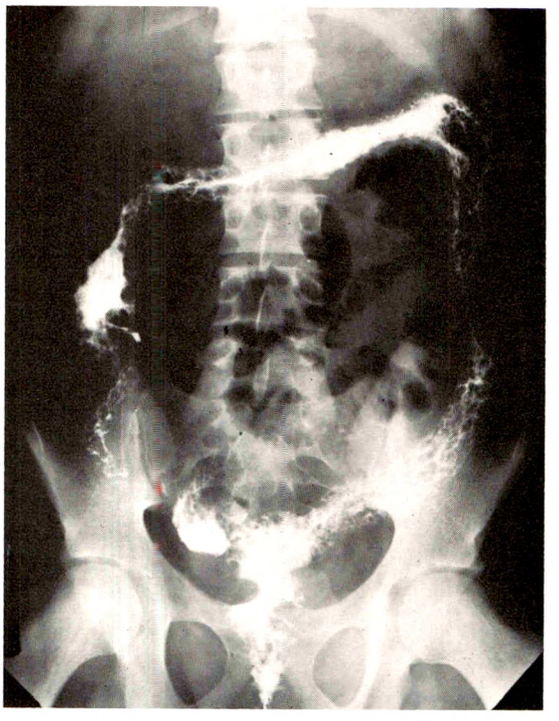


Fig. 9. Ulcerative colitis of entire colon with backwash ileitis. There is loss of haustration, shortening, and pseudopolyps throughout the colon. Proctoscopy showed characteristic changes of inactive, advanced ulcerative colitis.

TABLE IV

RESULTS OF SURGICAL TREATMENT: SEGMENTAL COLITIS

Pathologic Diagnosis	Total No.	Asymptomatic		Recurrence
		less than 5 yr.	5 yr. or more	
Segmental ulcerative colitis	5*	3	1	1
Crohn's colitis	2	0	2	0
Crohn's colitis with regional enteritis	8	3	1	4
Total	15	6	4	5

* Two patients could not be located for follow-up.

cases correspond to the descriptions of Crohn's disease and ulcerative colitis given by Warren and Sommers[13] and by Lockhart-Mummery and Morson.[5] The latter authors pointed out that granulomas with giant cells, although characteristic of Crohn's disease, are not essential for the diagnosis if the other findings, such as wall thickening, are typical. One of our cases confirmed this observation.

In our cases of segmental colitis without involvement of the small intestine, ulcerative colitis predominated over Crohn's colitis in the ratio of 7:2. This is contrary to the opinion of Cornes and Stecher[2] who stated that segmental involvement is less common in ulcerative colitis than in Crohn's colitis.

The locations of the lesions in this series are similar to those reported by others, including Wolf and Marshak.[14] Involvement of the splenic flexure alone is common for either condition. Also, in cases of regional enteritis, isolated inflammatory involvement of the sigmoid is often noted.* This, most likely, is due to the proximity of the sigmoid to the inflamed ileum.

Roentgenographic Features. From these cases, it was evident that roentgenography after barium enema administration was far superior to the small bowel examination in demonstrating the lesion in the colon. In the original interpretations, the roentgenogram after barium enema study was considered to be normal in only 4 cases, all cases of Crohn's colitis with regional enteritis in the ascending colon. Even in retrospect, the lesion in the colon could be identified on the roentgenograms in only 1 case.

Often, in either Crohn's colitis or segmental ulcerative colitis, there was an irregular deformity which was indistinguishable from a carcinomatous change within a segment of colitis.

As noted by Marshak and co-workers,[6] we found that the presence of stricture was more suggestive of Crohn's colitis than of ulcerative colitis, while the presence of pseudopolyps was more likely to indicate ulcerative colitis. Deep ulcerations or sinuses were not often seen in these cases, although Wolf and Marshak stated that these are more common in Crohn's colitis and that they are the forerunners of fistulas.

Other features, such as skip lesion, disease limited to the right side of the colon, and deep linear ulcerations, may be more suggestive of Crohn's colitis, but it is often hard to be sure in an individual case. However, if the appearance of the lesion is suggestive of Crohn's colitis, small bowel examination should be performed before surgical treatment is attempted. Marshak and his associates[4,14] stated that if Crohn's colitis is diagnosed there is no need to worry about carcinoma developing in the involved

* It is difficult to assess the incidence of such sigmoidal involvement in our series of cases since sigmoidal resection was rarely performed in the surgical treatment of Crohn's disease of the ileum.

segment. However, this presupposes an ability to diagnose Crohn's colitis accurately in the first place before one can feel safe about delaying surgical treatment of a lesion whose roentgenographic appearance is suggestive of carcinomatous change in an area of segmental colitis.

Clinical Features. In general, our clinical findings were in agreement with the experience of others. It appears that, on the average, Crohn's colitis occurs at a slightly younger age than does ulcerative colitis. Lindner and co-workers[4] found this in their cases. Most of the cases of Crohn's colitis began in patients in the third and fourth decades of life, and it sometimes began in the second decade, while the patients with ulcerative colitis were a decade older.

Duration of the disease before diagnosis and treatment is highly variable. Some patients experience mild, recurring symptoms with long periods of complete, spontaneous relief. These may require surgical treatment eventually because of roentgenographic evidence suggestive of carcinoma. In others, the disease may progress rapidly after the onset and may require resection in the first 6 months. Usually, segmental ulcerative colitis progresses more slowly than Crohn's colitis.

In our series, diarrhea occurred at one time or another in almost every case, and there was no apparent difference between the diarrhea of the ulcerative colitis and that of Crohn's colitis; however, Cornes and Stecher[2] reported that the diarrhea was worse in ulcerative colitis than in Crohn's colitis. Perhaps this is true in the diffuse form of ulcerative colitis. Although many of the patients in both groups reported finding blood in their stools occasionally, bleeding of significance was rare, a point noted by many including Neuman and co-workers.[10] However, severe bleeding may occur, as it did in 2 of our patients with segmental ulcerative colitis. Abdominal pain in the form of cramps was common in both groups.

Perirectal complications such as anal fistulas and abscesses were present in 9 of our cases. Neuman and co-workers[10] found these anal complications in 23 per cent of their cases of "segmental colitis," and Cornes and Stecher[2] stated that they are common in Crohn's colitis but rare in ulcerative colitis.

In our series, the results of surgical treatment were not as good in patients with Crohn's colitis with regional enteritis as they were in those with segmental ulcerative colitis or Crohn's colitis without regional enteritis in the small intestine. This has been reported by Lindner and co-workers[4] and by Cornes and Stecher.[2]

SUMMARY

In proven cases of segmental ulcerative colitis or segmental Crohn's colitis, roentgenograms after barium enema administration were accurate in detecting the lesion but were not completely reliable in differentiating the two conditions. Features such as sigmoid involvement, "skip lesions," stricture, or fistula are highly suggestive that the segmental colitis is due to Crohn's disease. It recurs frequently after resection, especially in younger patients. The pathologic features include gross thickening of the intestinal wall. Microscopically, there is inflammation of all coats, mucosal ulceration, and giant cell granulomas. Roentgenographically, there is evidence of mucosal ulceration, loss of haustration, irregularity of the lumen which may be narrowed, and, occasionally, strictures or fistulas. The appearance may suggest carcinoma. Involvement of the sigmoid colon or alternating normal and diseased segments in the colon are particularly suggestive of this condition.

Segmental ulcerative colitis occurred in slightly older patients compared to Crohn's colitis, and results after resection were more favorable. Pathologically, there is ulceration of the mucosa, crypt abscesses, and inflammation mostly limited to the mucosa and submucosa. Roentgenographically, the colon appears shortened in the

involved area with ulcerated mucosa, formation of pseudopolyps, and, often, irregularity of the process in the involved segment suggestive of carcinomatous change.

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Vol. 99, No. 1

GRANULOMATOUS COLITIS*

ROENTGENOLOGIC APPEARANCE AND COURSE OF THE LESIONS

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ROENTGENOLOGIC interest in inflammatory conditions of the colon has been focused mainly on classic ulcerative colitis. Less attention has been given to the diagnosis of granulomatous colitis, or Crohn's disease of the colon, although it ranks second in frequency among the inflammatory diseases of the colon.

The roentgenologic appearance of granulomatous colitis is not so well known as that of ulcerative colitis. The lesions in early stages of granulomatous colitis have not been described and analyzed in the radiologic literature, the authors in this field dealing with more advanced stages of the disease.[13,18]

The mode of extension of the lesions is still obscure and has lately been under debate.[1]

This paper is concerned with the appearance of lesions in early and advanced stages of granulomatous colitis and their course, as seen in follow-up studies using the double contrast method. The differentiation from ulcerative colitis will also be discussed to some extent.

MATERIAL AND METHODS

Since 1954 we have used the double contrast technique routinely in the examination of the colon. From 1954 to 1965 altogether 21,000 patients were examined with the method. The modification of the double contrast method that we employ in the examination of inflammatory conditions of the colon was described in 1961.[17]

During the above 11 year period, ulcerative or granulomatous colitis was diagnosed in 240 patients. In 50 (20.7 per cent) of these, granulomatous colitis was found or confirmed at operation or necropsy.

PATHOLOGY

The pathology of granulomatous colitis has been described by several authors;[7,11,15,16] therefore, only the main features will be reviewed.

The etiology of the condition is unknown.

The typical lesions are inflammatory granulomas, containing epithelioid cells. The granulomas are localized mainly to the submucosa and the muscularis. In these layers of the intestine, there is also sclerosing lymphangitis, causing edema of the bowel wall. Deep and undermining ulcers develop in the mucosa.

At operation, diseased segments of the bowel are found to be thick-walled and heavy. The mucosa of the resected specimens shows ulcers, and, in advanced cases, also numerous crowded polypoid nodules, arranged in parallel rows with longitudinal ulcers in between. This is known as the "cobble stone" appearance of the bowel. The lesions are not always continuous in the bowel.

Strictures often develop in granulomatous disease of the small bowel as well as of the colon. Complicating fistulae, caused by penetrating ulcers, are not uncommon. They may appear early or late in the course of the disease.

Cancer is not known to develop on the basis of granulomatous colitis.

ROENTGEN FINDINGS IN EARLY STAGES OF GRANULOMATOUS COLITIS

In granulomatous disease of the intestine, the lesions usually first appear in the terminal segment of the ileum. In all of our 50 cases of granulomatous disease of the colon, associated ileal lesions were found. We have never seen any case in which the

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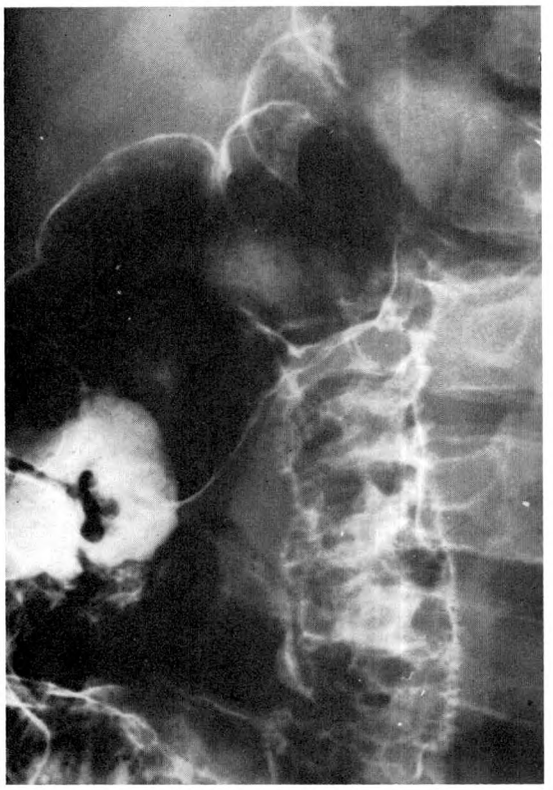


FIG. 1. Ulcers in granulomatous ileitis. Recurrence after ileocecal resection and transversostomy.

lesions were confined exclusively to the colon.

Although the diagnosis of the ileal lesions will not be discussed here, it should be mentioned that since the ileocecal valve was imcompetent in 40 of our 50 cases, good double contrast roentgenograms showing the lesions of the terminal ileum were often obtained. In patients who had been operated upon with ileo-transversostomy, ileal lesions were consistently well visualized (Fig. 1).

The granulomatous process may produce roentgenographically visible changes of the colon, when it is still confined to the terminal ileum. In 4 cases we found processes, bulging into the medial aspect of the cecum, that otherwise had a normal appearance (Fig. 2*A*). Subsequent examination of the small intestine revealed the lesions in the ileum. This change in the outline of the cecum occurred early, and was seen 1 to 4 months after the onset of symptoms.

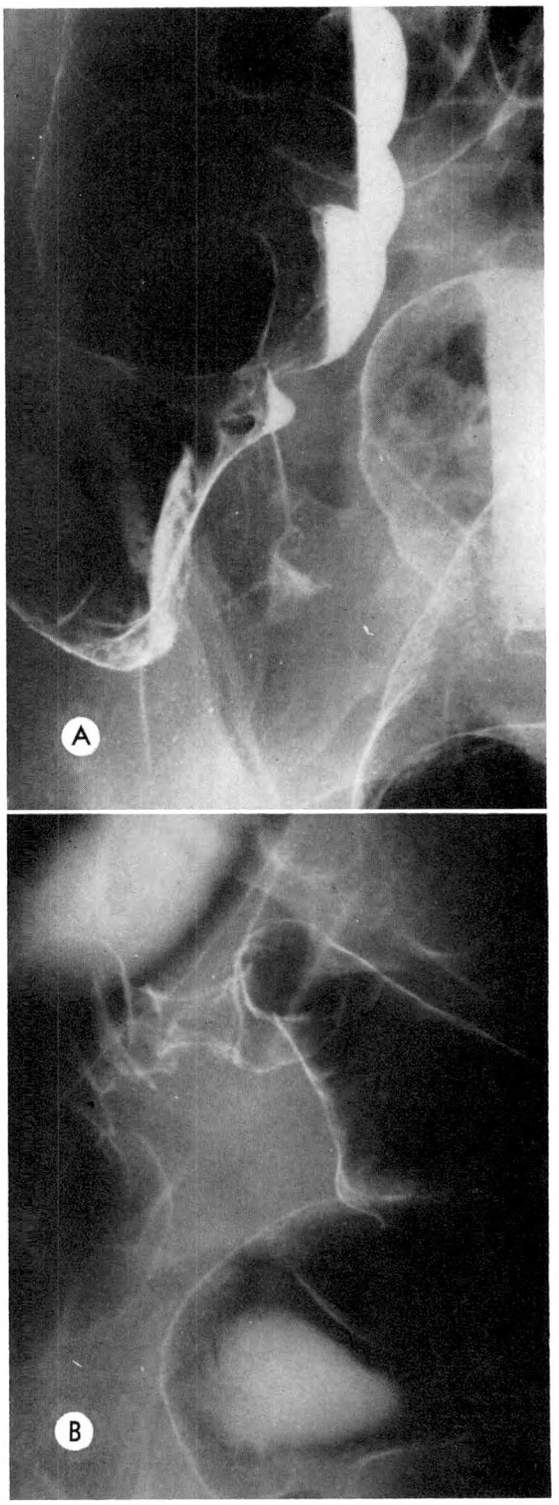


FIG. 2. (*A*) Granulomatous ileitis. Mass in the ileocecal region with a pressure defect of the medial side of the cecum. (*B*) Abscess originating from the ileum causing stricture of the distal part of the sigmoid.

In patients operated upon in this early stage, mostly because of suspected appendicitis, conglomerates of swollen lymph nodes were found at the ileocecal junction. In later stages of the disease, abscesses in this area may produce a similar picture. In 2 cases abscesses, originating from the ileum, have caused strictures of the bowel at the rectosigmoid junction, with no associated mucosal changes (Fig. 2*B*). These changes have been described by Theander and Wehlin[14] as a sign of a cicatrizing process outside the bowel wall, and are most commonly seen in endometriosis.

The lesions of *early granulomatous colitis* always appeared first in the right half of the colon.

In most of the cases that were examined shortly after the onset of symptoms, the lumen of the cecum was decreased but *without* any associated mucosal changes. Such narrowing is readily recognized in double contrast roentgenograms taken with the patient in the left lateral recumbent position and a horizontal beam. In this projection the cecum will normally be the most distended part of the colon. The narrowing is sometimes so striking as to be reminiscent of stenosing cancer of the colon (Fig. 3).

Of the 50 patients, 23 were examined within 1 year of the onset of symptoms, and all except 4 showed this type of change, *i.e.*, narrowing without coexisting mucosal alterations. The lumen was often not only narrow, but also shortened.

We have found the local narrowing of the bowel in early granulomatous colitis to be reversible, in contrast to the strictures in the late cicatrizing stages. In early cases, in which the patients were operated upon because of suspected appendicitis and later became symptom free, the narrowed part of the colon not only recovered its original caliber but also its original length (Fig. 4, *A* and *B*).

If, however, the disease progresses, ulcers will appear. Deep and penetrating ulcers are known to be characteristic of granulomatous colitis. Yet, in some of our cases, small coniform ulcers were seen in the acute stage (Fig. 5*A*). They were not crowded, but distinctly separated. They sometimes involved extensive areas of the intestinal wall. These small ulcers were observed only for a short time during the course of the disease. At a subsequent examination, they had in most cases become deep and broad.

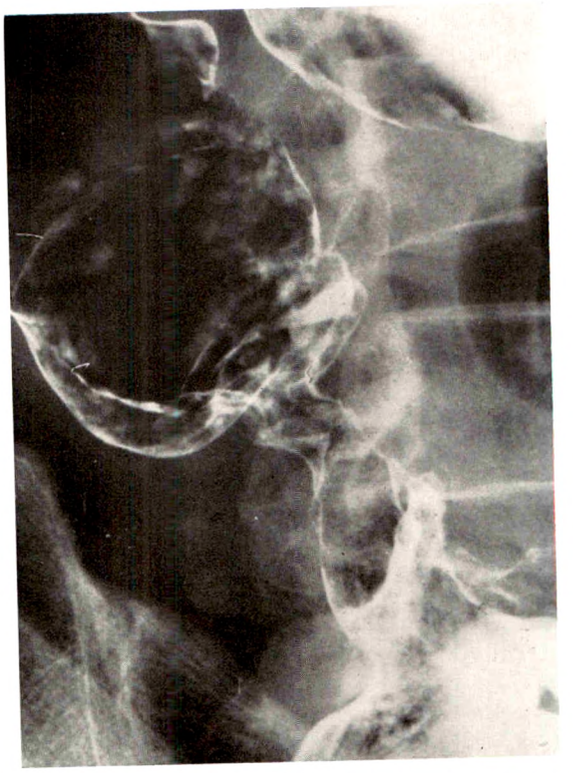


Fig. 3. Granulomatous colitis. Stricture of the cecum reminiscent of cancer.

However, in a few cases the small ulcers proved to be reversible, and in 2 cases the ulcers disappeared although they were fairly widespread.

In most cases, but not in all, the development of the small ulcers was accompanied by a narrowing of the lumen of the affected segment of the colon.

Roentgen Findings in Advanced Stages of Granulomatous Colitis

If the disease progresses, the ulcers become larger, deeper, and elongated. They will often undermine the mucosa, and then a double outline of the colonic wall will be seen in the roentgenogram (Fig. 7*A*; and 9*B*).

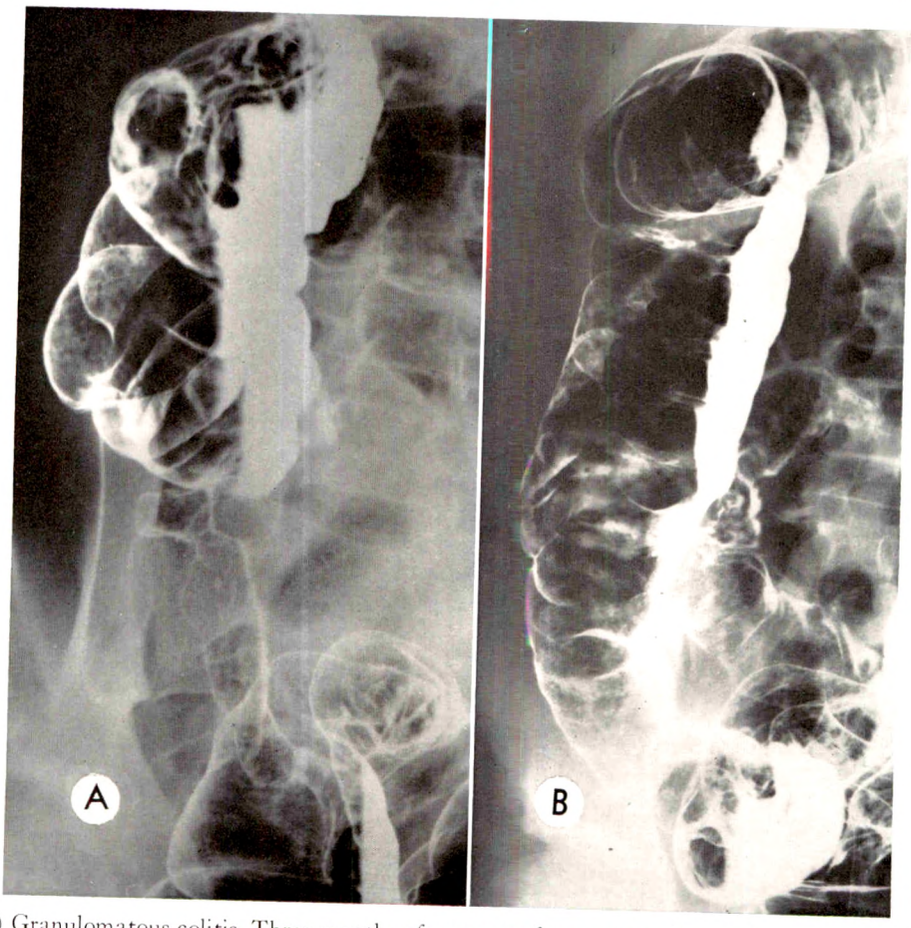


FIG. 4. (*A*) Granulomatous colitis. Three months after onset of symptoms. Shortening and narrowing of the cecum and ascending colon. No mucosal lesions visible in the colon. Ileitis. (*B*) Same case 4 months later. The cecum and ascending colon are of normal width and length. Resection of distal ileum performed.

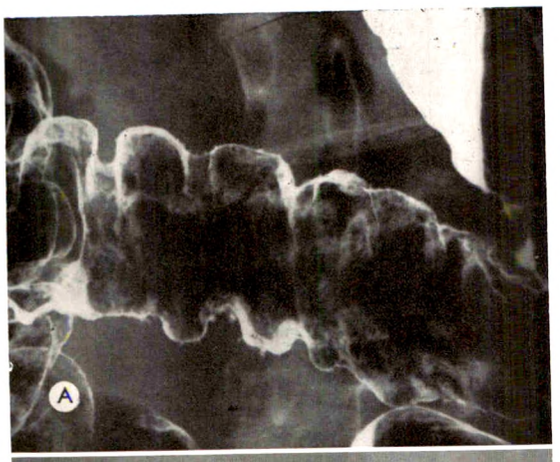
In the small bowel, granulomatous disease has a tendency to develop fistulae, especially after surgical procedures. Perforation of the large bowel may also occasionally occur. In our cases, however, deep abscesses in the bowel wall were more common. The abscesses were found mostly in the transverse and descending segments of the colon (Fig. 6). As a rule, the ulcers were also deepest in these areas.

A further typical change in advanced cases of granulomatous colitis is the above mentioned "cobble stone" appearance of the colon. The crowded inflammatory nodules, as well as the longitudinal, serpiginous ulcers in between, are distinctly visualized by the double contrast technique. The agreement between the roentgenogram and the resected specimen is illustrated in Figure 7, *A* and *B*.

In none of our cases did the deep, penetrating ulcers disappear, nor did we observe any regression of the lesions when they had reached the "cobble stone" stage.

The further course of the disease in our cases was characterized by a deepening of the ulcers and supervention of irregular strictures. Local stenosis in the transverse or the descending segments of the colon occurred, but in most cases stricturing began in the cecum and advanced distalwards.

We have not been able to recognize any typical "final stage" of granulomatous colitis. The disease in advanced stages always showed extensive changes of varying severity.



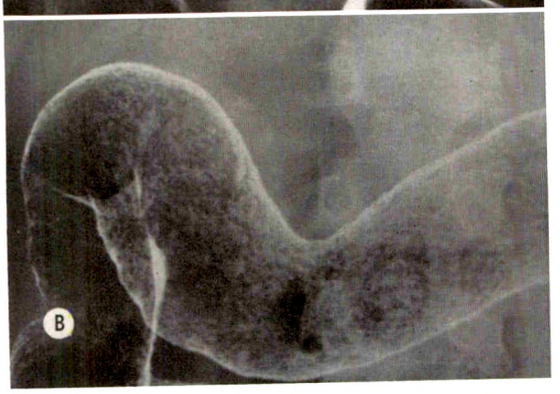




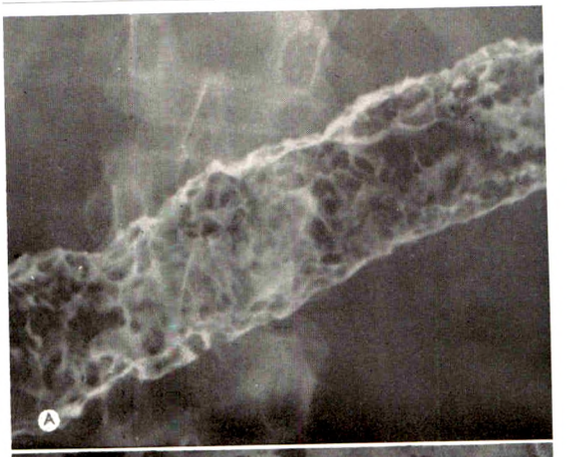
Fig. 6. Deep abscesses in the bowel wall in advanced granulomatous colitis.

Fig. 5. (*A*) Granulomatous colitis. Small coniform discrete ulcers in early stage of the disease. (*B*) Ulcerative colitis. Crowded shallow ulcers and granular appearance of the mucosa.

Lesions of the Rectum

We have not seen extension of granulomatous lesions to the rectum at roentgen examination. All those patients who had undergone resection were proctoscoped on several occasions, and the findings were always in accord with the roentgen observations.

On the other hand, we have, at routine examination, been able to demonstrate anal and ischiorectal fistulae that are typical of the disease and are often the cause of the patient's initial complaints (Fig. 8). This was, however, not always possible.



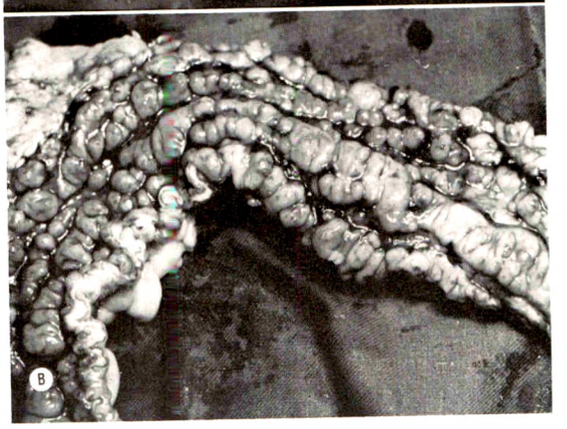


Fig. 7. (*A*) "Cobble stone" appearance and deep serpiginous ulcers in granulomatous colitis. (*B*) Resected specimen.

MODE OF EXTENSION OF LESIONS IN GRANULOMATOUS COLITIS

Forty-five of the 50 patients were examined on more than one occasion, 4 of them more than 5 times. We had the opportunity of following-up the patients for a long period, often from shortly after the onset of symptoms.

During such follow-ups, we were able to observe whether the lesions remained localized to one and the same segment in the colon, or whether the process was able to spread.

In all those patients who later developed widespread changes in the colon, we could, if we had followed the disease from an early stage, observe that the process is capable of extending aborally from the ileum and the proximal colon. When such extension occurred, it did so within the first 2 years after the onset of symptoms (Fig. 9, *A* and *B*). The spread was thus found to be an early feature of the disease. In 4 cases such spreading of the process in the colon occurred within 1 year after the detection of the first visible cecal lesions.

The process always spread by continuity. In some cases, however, lesions that were not too advanced were seen to disappear in one segment of the colon, while progression occurred in a segment aboral thereto (Fig.

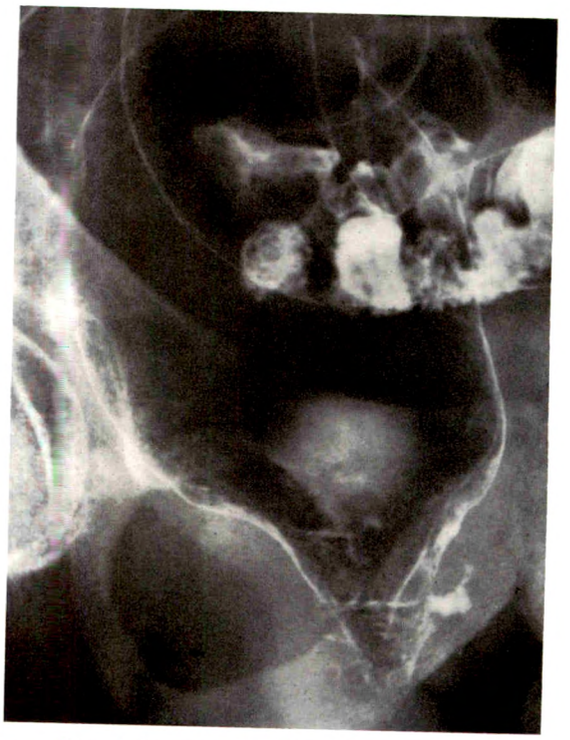


FIG. 8. Anal fistulae. No mucosal lesions in the rectum.

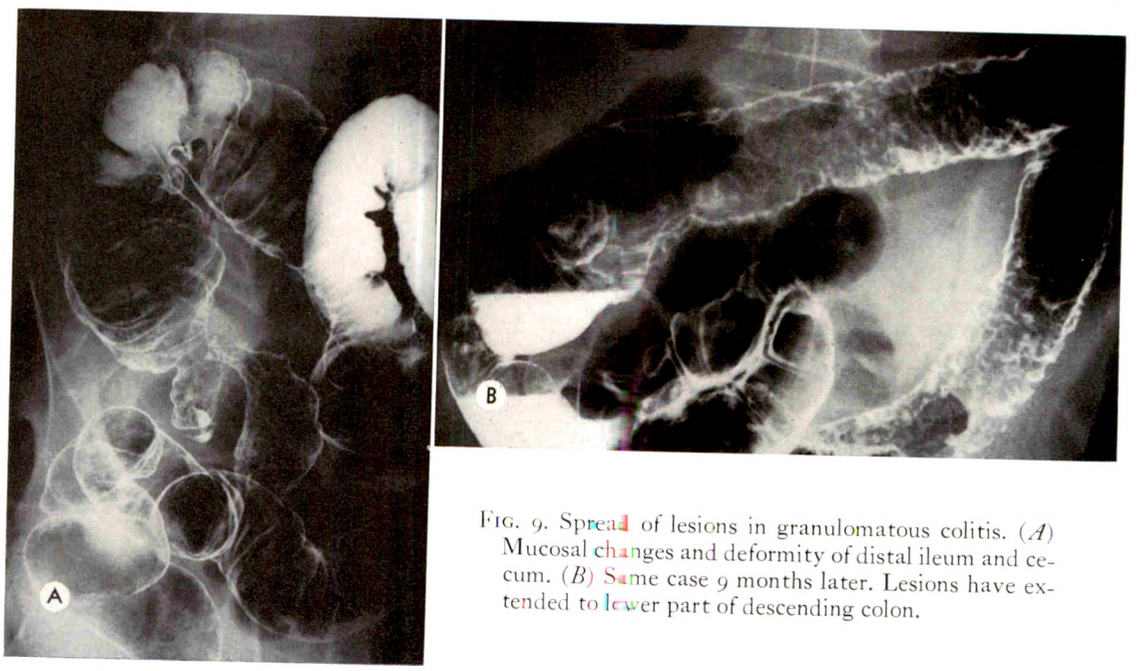


FIG. 9. Spread of lesions in granulomatous colitis. (*A*) Mucosal changes and deformity of distal ileum and cecum. (*B*) Same case 9 months later. Lesions have extended to lower part of descending colon.

10, *A* and *B*). Then, at later examinations an apparently normal part of the colon was seen proximal to diseased parts. In the case shown in Figure 10, *A* and *B*, the continuity of the process in the ileum and in the colon is interrupted by the normal appearance of the cecum and ascending colon.

DISCUSSION

INCIDENCE AND FREQUENCY

The literature gives no precise information on the incidence of granulomatous disease, presumably because the patients tend to be referred to certain large centers. For example, in 1954 van Patter *et al.*[10] at the Mayo Clinic reported as many as 600 cases of Crohn's disease, 30 per cent of which had lesions of the colon, while Meyers *et al.*[8] reported only 13 cases for a 12 year period in a hospital with 18,000 admissions per annum.

Our 50 consecutive cases were seen during an 11 year period in Malmö, Sweden. This city has 240,000 inhabitants and is served by only 1 hospital. Presumably, every case of long-standing disease of the colon will sooner or later be examined at our X-ray department.

Few estimations have been made of the ratio between ulcerative and granulomatous colitis. One reason for this may be that it is often difficult to distinguish between the two conditions, especially clinically. In Crohn's[1] own patients with inflammatory disease of the ileum and the colon, about 12 per cent had granulomatous colitis. According to Neuman *et al.*[9] regional colitis is estimated to represent 4 to 10 per cent of all cases of colitis. In our material this figure was 20.7 per cent. Thus, granulomatous colitis must be regarded as a fairly common type of colitis in our population.

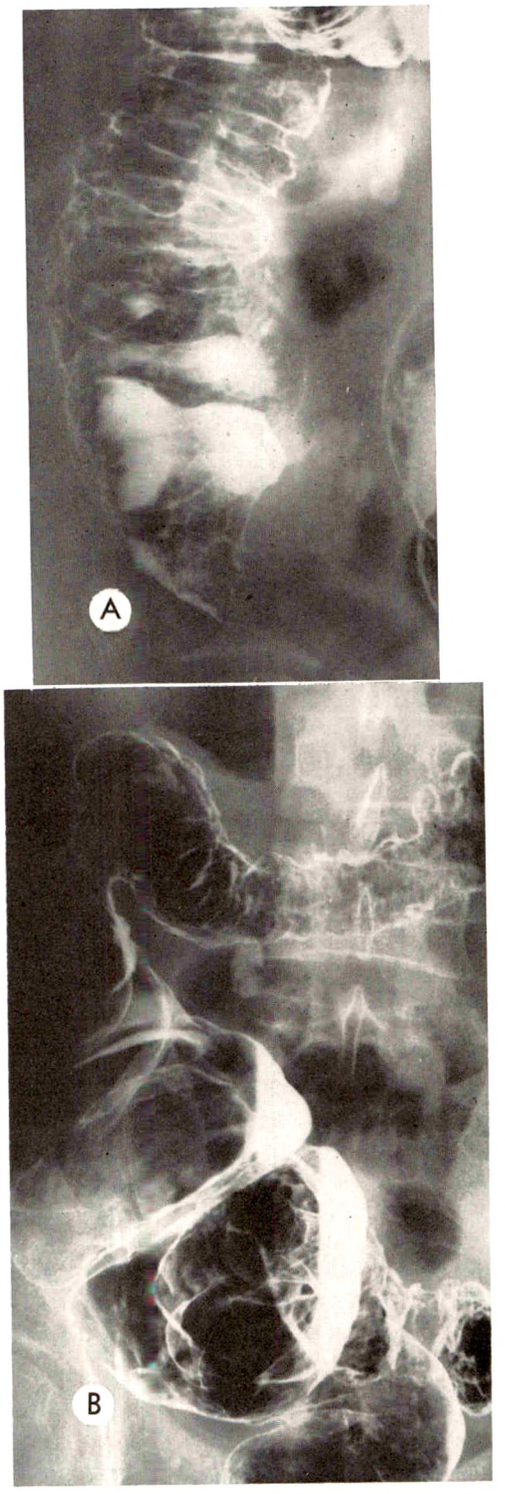


Fig. 10. Development of discontinuous lesions in granulomatous colitis. (*A*) Small ulcers and deformity of the cecum and ascending colon 3 months after onset of symptoms. (*B*) Same case 12 months later. Lesions in the cecum and ascending colon have disappeared. New lesions in the hepatic flexure and transverse colon. Ileal lesions visible.

LESIONS IN GRANULOMATOUS COLITIS

No unanimity has been achieved regarding the localization of lesions in granulomatous disease of the small bowel and of the colon. In a series reported by Cornes and Stecher,[5] the lesions were only demonstrated in the colon, while in van Patter and coworkers'[10] large series, coexisting lesions were invariably found in the ileum. Our experience agrees with that of van Patter *et al.*

When Colp[4] in 1934 reported the first operated case of Crohn's disease in the colon, he observed, besides changes of the ileum, "a spastic contraction" of the cecum. That diseased segments of the colon become narrow in granulomatous colitis has since been described several times, but always in association with severe changes of the mucosa.[13,18] According to Warren and Sommers,[16] the process, at least in the beginning, is confined to the submucosa with thickening of the intestinal wall and narrowing of the lumen. This may explain our findings that the cecum appears narrow in early stages, although the mucosa shows no change.

Clinical regression of acute Crohn's disease is reported in juvenile[12] as well as adult patients.[15] This is corroborated by our findings, although no roentgenographically verified instances of regression in granulomatous colitis have previously been published. As far as we know, this is the only disease of the colon in which a reversible narrowing and shortening of the cecum has been observed.

Sutcliffe[13] stresses that the typical ulcers in this disease are deep and penetrating, and that the small disseminated ulcers, characteristic of ulcerative colitis, do not occur in granulomatous colitis. The small ulcers that we observed have previously escaped detection. This may be explained in part by the fact that they are not readily recognized with conventional colon examinations, and partly because they retain this form only for a short time.

From the clinical point of view, it is important to know whether a lesion is reversible or not. Surgery is not indicated if regression can be expected from conservative treatment. In our experience, all those lesions described under the heading "lesions in early stages" are reversible, although in many cases progression occurred.

The presumably irreversible lesions described under the heading "lesions in advanced stages" have been studied by previous authors. Our findings are in agreement with theirs, although we believe that the double contrast technique gives more detailed information on the appearance and extent of the lesions. The examination carries no undue harm or risk to the patient.

DIFFERENTIATION FROM LESIONS IN ULCERATIVE COLITIS

The symptoms of granulomatous colitis and ulcerative colitis are largely similar, and clinical differentiation between the two conditions is often not possible. According to Wolf and Marshak,[18] in advanced cases it may be difficult to distinguish between them even roentgenographically.

Yarnis and Crohn[19] state that they may occur simultaneously in different parts of the colon. Thus, in 1949 Crohn[6] reported this combination in 22 of 306 cases.

This opinion is in contrast to that of Lockhart-Mummery and Morson,[7] who claim that granulomatous and ulcerative colitis are entirely different conditions and that they cannot coexist. This view is being more and more widely accepted.

Distinction between the two conditions is not only of theoretic, but also of practical interest. Surgically, granulomatous colitis often requires only a limited bowel resection as opposed to the disabling proctocolectomy necessary in extensive ulcerative colitis. The latter disease also carries a marked risk of development of malignant growths in the colon. Control examinations must, therefore, be made on these patients at regular intervals.

In ulcerative colitis it is, above all, the mucosa that is affected. In the beginning the ulcers are shallow. Later, they may penetrate into the submucosa and muscularis, but perforation is rare. The ulcers often erode large areas of the mucosa.

The roentgen findings in ulcerative colitis have been discussed elsewhere.[17] Here, they will be only briefly reviewed for comparison with those in granulomatous colitis.

The localization of the lesions is different in the two conditions. In ulcerative colitis, the changes are most commonly found in the rectum and sigmoid. They may be confined to segments above the rectum, but this is uncommon. In younger patients, the whole colon and rectum may be affected simultaneously at the beginning of the disease. The lesions are always continuous.

In contrast, in granulomatous colitis, lesions in the early stages are confined to the right half of the colon. Later they may extend to the sigmoid, but we have not observed spread to the rectum. The lesions in granulomatous colitis are not always continuous.

The granular appearance of the mucosa, which may be seen in roentgenograms of early cases of ulcerative colitis, is not observed in granulomatous colitis.

The ulcers in ulcerative colitis are closely crowded and often very shallow (Fig. 5*B*). They may retain this appearance for a long time.

In granulomatous colitis, the small ulcers that we have observed were seen only in the acute stage. They are coniform and discrete. They were seen only for a short time. At subsequent examinations, they had either disappeared or become deeper and broader.

Although the ulcers in ulcerative colitis deepen in advanced disease, this is much more pronounced in granulomatous colitis. The appearance of the ulcers is, however, rather similar in moderately advanced stages of the two conditions. Deep ulcers in the rectum are often seen in ulcerative colitis, but not in granulomatous colitis.

On the other hand, the "cobble stone" appearance of granulomatous colitis is not seen in ulcerative colitis. Instead, in advanced ulcerative colitis, remnants of inflamed mucosa can be seen on the surface of the bowel, otherwise eroded by the ulcerative process. In typical cases such "pseudopolyps" of ulcerative colitis are much sparser than the "cobble stones" of granulomatous colitis. They are, in addition, more irregular in outline and may somewhat resemble residual fecal matter (Fig. 11).



Fig. 11. Ulcerative colitis. Pseudopolyposis (not fecal matter) in long standing disease.

The "burnt-out" stage of ulcerative colitis with complete erosion of the mucosa and advanced shortening of the bowel is not seen in granulomatous colitis. In advanced cases of the latter disease, severe ulcerative lesions were always found.

Spread of Lesions in Granulomatous Colitis

Most authors agree that the lesions in granulomatous colitis are probably stationary, *i.e.*, they do not spread to adjacent segments of the bowel. Bockus[2] states that he never observed the progressive creeping downward from the initial lesions in the terminal ileum or proximal colon except in recurrences following operation. That such spread of the process really occurs has been demonstrated above. When it was observed, it occurred early in the course of

the disease. The lesions usually spread rapidly, and in some cases more rapidly than in any of our cases of ulcerative colitis. According to Bockus,[2] the majority of cases have a long history before roentgen examination of the colon is made. This may explain why the migrating nature of the disease has not been observed before.

There is general agreement that so-called skipped areas are typical of granulomatous colitis.[3,13] This means that affected parts of the bowel are separated by unaffected parts. This discontinuity of lesions in the colon gives the impression that the process, during its development, may spare smaller or larger parts of the bowel.

We have, however, not observed lesions to develop simultaneously or independently in different parts of the colon.

When we had the opportunity of following the spread of the lesions aborally in the colon, the spread was always uninterrupted. As was shown above, the lesions in some cases disappeared in one area of the colon, while they progressed in adjacent distal segments. At subsequent examinations, it then appeared as if one segment of the colon had been "skipped" by the process.

On the basis of these observations, we feel that the so-called skipped areas are apparent rather than real. They can be regarded as a local healing of the process in a disease that is essentially migrating.

SUMMARY

Observations made in a study of lesions in a consecutive series of cases of granulomatous colitis in various stages of the disease, especially in the early stages, showed not only that certain lesions are reversible, but also that the process can spread rapidly. The development of discontinuous lesions is illustrated and explained.

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VOL. 99, NO. 1

ULCERATIVE DISEASE OF THE INTESTINAL TRACT PROXIMAL TO PARTIALLY OBSTRUCTING LESIONS*

ROENTGEN APPEARANCE

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THE purpose of this communication is to direct attention to the fact that inflammatory changes occasionally occur in the bowel proximal to partially obstructing colonic malignancies. These inflammatory changes may mask the presence of the primary disease and lead to errors in diagnosis. Demonstration of this secondary bowel inflammation may alert one to the existence of an obscure partially obstructing lesion. Three patients with partially obstructing colon carcinoma, 2 in the sigmoid and 1 in the cecum, with positive roentgen findings are reported.

REVIEW OF LITERATURE

Hurwitz and Khafif[8] reported 13 patients who had acute necrotizing colitis proximal to a carcinoma of the colon which had caused incomplete large bowel obstruction. Patients with a past history of ulcerative colitis or other subacute and chronic disease of the colon were excluded from this series. In a discussion of malignant degeneration in ulcerative colitis, Kasich, Weingarten and Brown[9] stated that, in some patients with obstructing carcinoma of the colon, ragged ulcerations which may be indistinguishable in the late stages from the ulcers of ulcerative colitis may be found proximal to the carcinoma. Dennis and Karlson[3] mentioned 4 patients with cancer of the left colon in whom anatomic studies of resected bowel showed areas of apparently classic idiopathic ulcerative colitis proximal but not distal to partially obstructing cancers. Glotzer, Roth and Welch[5] describe 6 patients with acute ulcerative colitis proximal to a partially obstructing cancer of the colon. Five of these patients were found only after a retrospective study of 1,886 cases of colon carcinoma seen over a 12 year period. Goulston and McGovern[6] reported 5 patients with severe pseudomembranous ulcerative colitis associated with partially obstructing lesions of the rectum and sigmoid.

Although there are reports of clear-cut obstruction at the ileostomy stoma without complicating ileitis following total colectomy for either inflammatory or neoplastic disease, there is evidence incriminating obstruction as one cause of prestomal ileitis. Warren and McKittrick[12] have suggested that the supposed ascending enteritis proximal to an ileostomy is very likely the result of the surgical construction of a poor stoma. They cited 2 patients in whom ileostomy had been performed in conjunction with total colectomy for familial polyposis and who subsequently developed a classic picture of ascending enteritis. Thayer and Spiro[10] reported 4 patients with ileitis that developed proximal to an ileostomy. Because examination of the ileum at the time of surgery showed no gross or microscopic evidence of disease, it would appear that this ileitis was not the result of previously unrecognized ileal disease.

A severe, often fatal, nonspecific enterocolitis may result from the functional obstruction of the aganglionic megacolon in Hirschsprung's disease. Bill and Chapman[1] believe that the enterocolitis of Hirschsprung's disease is related to partial intestinal obstruction. Furthermore, correction of the obstruction by colostomy relieved the enterocolitis. Hope, Borns and Berg[7]

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were aware that a significant percentage of infants with Hirschsprung's disease have fulminating gastroenteritis or chronic diarrhea with failure to thrive. A severe form of exudative enteropathy is occasionally seen secondary to the obstruction caused by the aganglionic segment. In these patients, the proximal bowel is thickened, nodular and edematous with the roentgen appearance which mimics ulcerative colitis. It has been suggested that diarrhea seen in fecal impaction is a symptom dependent on bowel changes proximal to the obstructing stool rather than to the local irritation of the impacted stool.[1]

ROENTGEN FINDINGS

The roentgen appearance of the ulcerated bowel proximal to partially obstructing lesions of the colon has not been described in the available literature, presumably because of its rarity and because contrast studies of the colon in this condition are limited or omitted. The involved segment of large bowel shows irregular narrowing, absence of normal mucosal pattern and isolated discrete ulcerations. The transition between normal and diseased bowel is abrupt. There is evidence of stasis and at times, deep, broad, circular contractions. In the small bowel, the changes simulate regional ileitis with an irregular caliber of the bowel, mucosal edema and segmentation. Stasis is evident with occasional areas of moderate dilatation. In the differential diagnosis, retrograde spread of carcinoma into the ileum must be excluded. This usually appears as a short, localized stenotic segment immediately proximal to the ileocecal valve.

After these 3 reported cases came to our attention, a study was made to determine the prevalence of these roentgen abnormalities. The records of 176 patients with the discharge diagnosis of carcinoma of the colon at the Jewish Hospital of St. Louis during the period from January, 1962 to June, 1965 were reviewed. Patients with

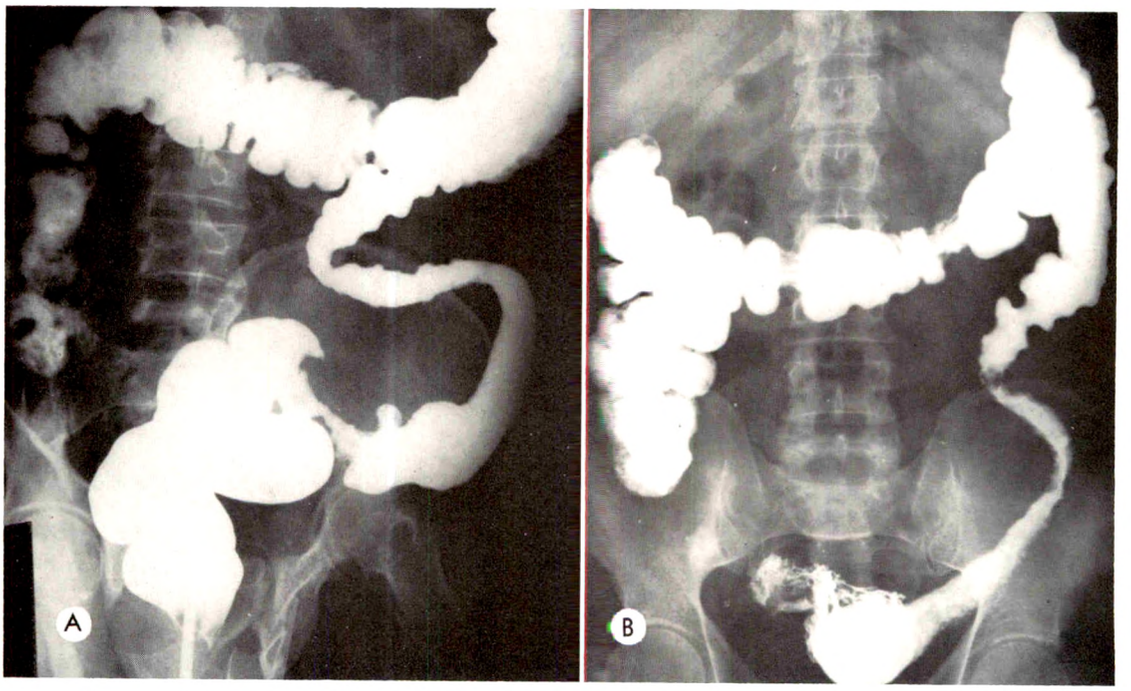


FIG. 1. Case 1. (*A*) The filled colon and (*B*) the postevacuation roentgenograms showing the large annular carcinoma of the sigmoid and the changes proximal to the lesion simulating ulcerative colitis. The bowel lumen is irregularly narrowed, with mucosal alteration and suggestive ulceration. There is evidence of stasis in the bowel proximal to the obstructing lesion. The transition between normal and diseased bowel proximally is abrupt.

idiopathic ulcerative colitis were excluded. There were 75 patients who had partially obstructing lesions that were visualized preoperatively by barium enema. In this series, not 1 case was found with unequivocal roentgen changes in the prestenotic segment similar to those described in this report.

REPORT OF CASES

Case 1. A. L., a 63 year old white male, was admitted with a history of moderate constipation of 3 years' duration. During the 2 weeks immediately prior to admission the patient developed nausea, generalized cramping abdominal pain, increasingly severe diarrhea, and the passage of bloody stools. Physical examination including sigmoidoscopy was unremarkable. Barium enema examination showed a napkin-ring narrowing in the mid-sigmoid colon charactreistic of carcinoma (Fig. 1, *A* and *B*). There were changes in the proximal sigmoid and descending colon suggestive of segmental ulcerative colitis. After reviewing an air-contrast barium enema examination performed almost 2 years earlier, it was possible to establish the fact that an unrecognized sessile lesion of the mid-sigmoid had been present and that the bowel proximal and distal to the lesion was entirely normal (Fig. 2). At operation, a constricting lesion of the sigmoid colon, measuring about 7 cm. in length, was found and 20 cm. of bowel proximal to the lesion was noted to be "somewhat thickened." Examination of the mucosa of the transverse and ascending colon with the proctoscope at the time of surgery was unremarkable.

The pathologic specimen consisted of 65 cm. of sigmoid and descending colon, the distal 12 cm. of which appeared entirely normal. The tumor involved the entire circumference for a distance of 5 cm. Proximal to this, 3 cm. of normal bowel was noted. More proximally for a distance of 35 cm., the entire circumference of the bowel was involved in a diffuse process which appeared to resemble ulcerative colitis. The surface was granular and reddened and several polypoid growths were noted in the area of the colitis. The inflammatory process ended abruptly at the upper end of the specimen where 10 cm. of normal appearing bowel was present. Microscopic examination showed that the tumor was a moderately differentiated adenocarcinoma. The ulcerated area contained sharply demarcated ulcers with a loss of mucosa and chronic inflammatory granulation tissue replacing the mucosa in many areas. Although no metastatic involvement was noted at the time of surgery, the patient subsequently developed liver metastases and expired.

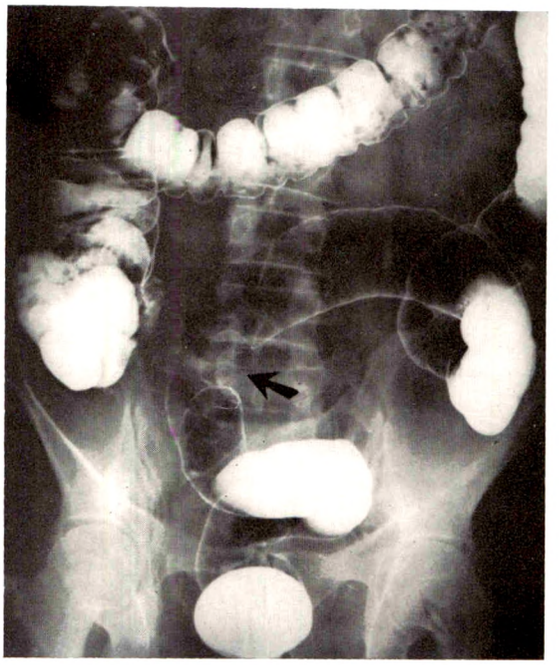


Fig. 2. Case 1. An air-contrast examination of the colon showing the sessile lesion in the sigmoid with entirely normal appearing bowel both proximal and distal to it.

Comment. This is the case of a 63 year old white male with a neoplasm of the sigmoid known in retrospect to be present for almost 2 years, who, in the 2 weeks immediately prior to hospital admission, developed symptoms indicative of an acute ulcerative colitis. An acute inflammatory process was found at surgery to involve approximately 35 cm. of the descending colon proximal to the large obstructing annular carcinoma.

Case 11. M. S., a 68 year old white female, was admitted in March, 1965 with a history of cramping abdominal pain for 3 weeks and fever for 1 week prior to admission. She had vomited one time on the afternoon of admission. There was no past history of previous abdominal operations. The admission temperature was 103° F. The abdomen was soft, but there was tenderness without rebound pain in the left lower quadrant. The bowel sounds were nor-

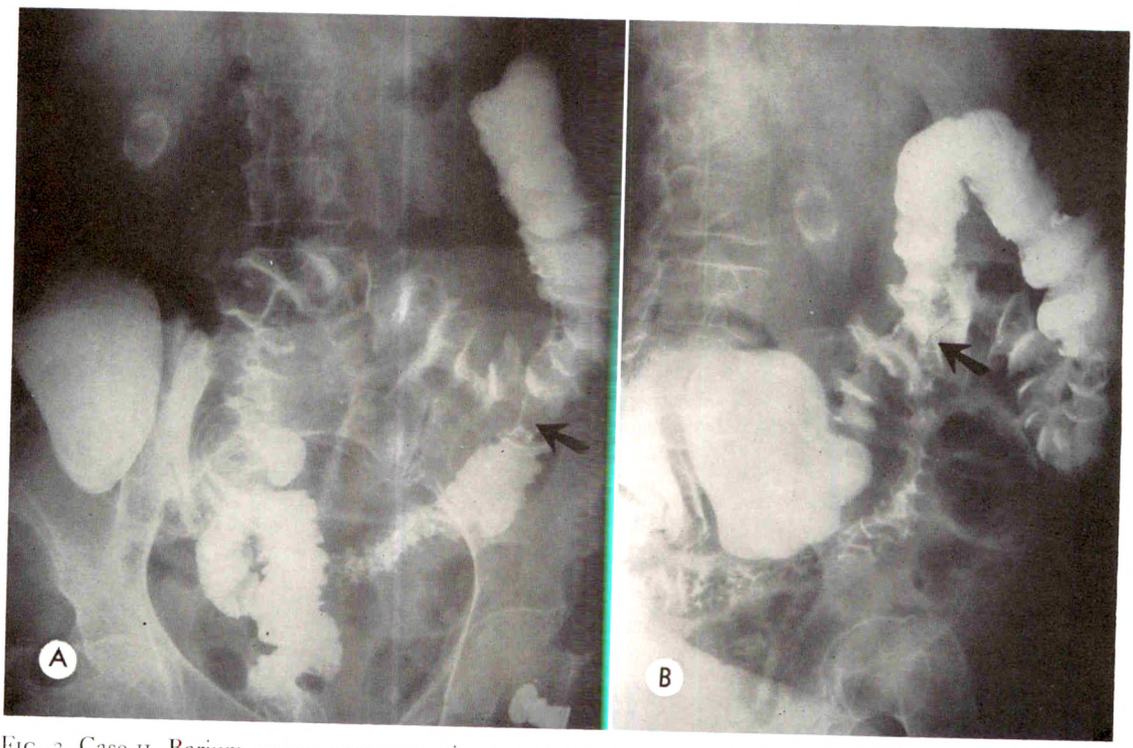


FIG. 3. Case II. Barium enema postevacuation roentgenograms. (*A*) Anteroposterior and (*B*) left posterior oblique projection. The annular constriction is shown in the descending colon (arrow). There are changes in the bowel proximal to the lesion simulating ulcerative colitis with deep broad circular contractions of the major portion of the transverse colon.

mally active. The white blood cell count was 13,500 with a rather marked shift to the left. After admission, the patient passed several grossly bloody stools. A barium enema examination 2 days later showed partial obstruction of the descending colon by an annular lesion. The bowel immediately proximal to the obstruction was irregularly narrowed with a shaggy contour and suggestive ulceration. Proximal to this segment which simulated ulcerative colitis, there was a much longer portion extending to the hepatic flexure which showed broad, deep circular contractions (Fig. 3, *A* and *B*). Widespread carcinomatosis was discovered on exploration and only a limited resection was performed. The specimen measured 59 cm. in length, half of which was proximal to the obstructing lesion which was a submucosal tumor constricting the lumen to a diameter of approximately 1 cm. In the proximal bowel, there were multiple ulcers, absence of normal mucosa and many 1–5 mm. sized raised tan nodules between the areas of ulceration. Microscopic examination proved the tumor to be a mucin-producing adenocarcinoma metastatic to the intestinal wall. The proximal colon showed extensive mucosal ulceration with fibrosis of the submucosa and hypertrophy of the muscularis. There were both chronic and acute inflammatory cells in the submucosa and mucosa. The patient was readmitted in July, 1965 and died. Autopsy revealed a primary peripheral adenocarcinoma of the right lung with widespread metastatic involvement.

Comment. This was an elderly female with a fairly recent history of cramping abdominal pain, fever and grossly bloody stools on several occasions. A high degree of obstruction was found in the descending colon which subsequently proved to be due to metastatic adenocarcinoma from a primary lung cancer. The bowel proximal to the obstructing metastasis showed, on exploration, extensive mucosal ulceration and evidence of both acute and chronic inflammation.

CASE III. R. F., a 58 year old white male, was admitted in November, 1964, with a history of intermittent mid-abdominal cramping pain of

approximately 8 months' duration. This became more severe in the week prior to admission when nausea and vomiting were first noted. There was no melena, diarrhea or bloody discharge. Following complete gastrointestinal studies, a diagnosis of terminal ileitis with cecal involvement was made by his private physician (Fig. 4*A*). Physical examination on admission showed that the abdomen was protuberant and tympanitic. Bowel sounds were normally active and somewhat high pitched. There was slight tenderness without rebound to deep palpation in both lower quadrants. Stool was positive for occult blood. The white blood cell count was 19,000 with 84 per cent polymorphonuclear cells and the hemoglobin was 12.7 gm. per cent. Roentgenograms of the abdomen showed findings indicative of high grade small intestinal obstruction. A Cantor tube was passed and barium was introduced into the distal ileum, demonstrating multiple narrowed loops of ileum with effacement of mucosa and skip areas which confirmed the earlier diagnosis of extensive terminal ileitis (Fig. 4*B*). The cecum on this examination was incompletely visualized.

At operation, the distal 3 feet of small intestine were involved in a brawny edematous process, typical of that observed in regional enteritis. Further exploration revealed that the cecum contained a hard mass which proved to be carcinoma. An ileotransverse colostomy was performed. Examination of the resected specimen showed that the wall of the terminal ileum was thickened and the mucosa was ulcerated. On microscopic examination, ulceration and inflammatory changes extending through the muscularis were found. The patient was readmitted on August 15, 1965 with recurrent carcinoma extending into the abdominal wall.

Comment. In this case the preoperative diagnosis of carcinoma of the cecum was not made because of the marked inflammatory changes in the distal ileum proximal to the obstructing carcinoma. A diagnosis of regional ileitis had been made on preoperative roentgen examinations. This was erroneously presumed to be the etiology of the small intestinal obstruction.

DISCUSSION

In considering the pathogenesis of the acute necrotizing colitis, most authors feel that partial obstruction, stasis and infection play important roles. The effect of experimentally produced bowel distention on the blood vessels of the bowel wall was

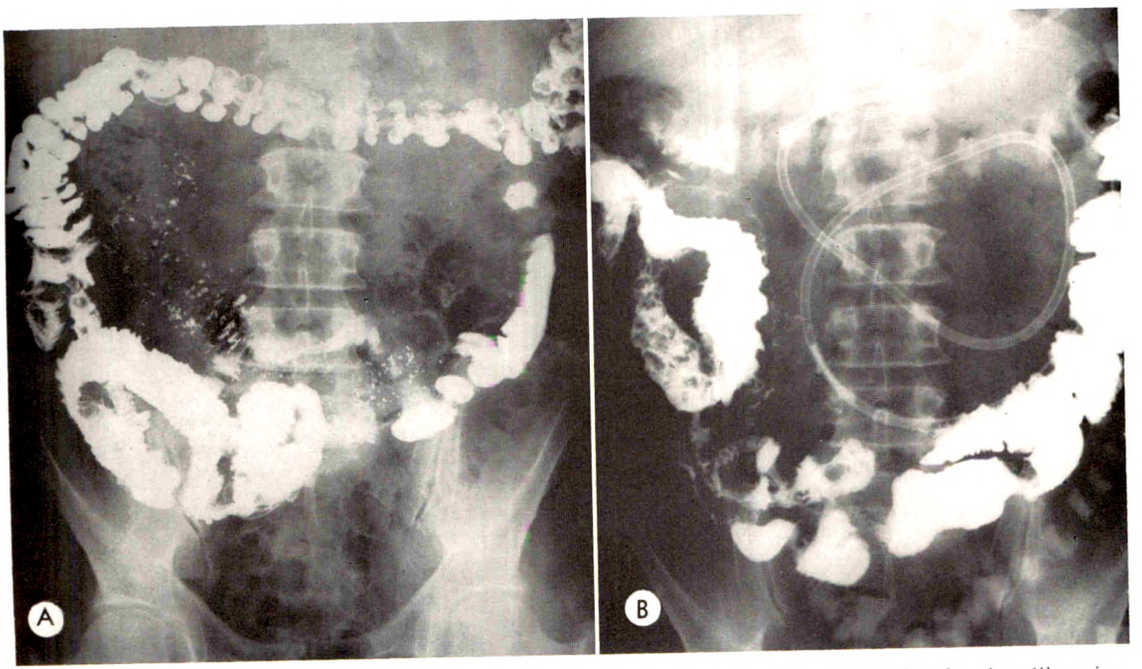


Fig. 4. Case III. (*A*) A 4 hour progress roentgenogram of an upper gastrointestinal series showing dilatation, mucosal alteration and stasis. The cecum is not well defined. (*B*) Study made with barium injected through the Cantor tube shows the same changes noted in the terminal ileum 10 days earlier.

studied by Van Zwalenburg,[11] who noted arrest of first capillary and later arteriolar and venular circulation in the distended bowel wall. The resultant ischemia of the mucosa and muscle was followed by infection and necrosis. Inflammatory changes and ulceration similar to ulcerative colitis have been experimentally produced by partial obstruction of the colon in dogs by Glotzer and Pihl.[4] It is their opinion that ischemia rather than fecal flora is the major causative factor in the development of these changes.

In acute obstruction of the colon, mortality rises with increasing duration of the intestinal distention. The pathogenic sequence is distention, with decrease in blood flow through the vessels extending from the mesenteric border to the bowel wall, mural thrombosis, ulceration, infection and perforation. Hypermotility, spasm and edema of the muscular wall secondary to the obstruction contribute to the impairment of the transmural blood supply of the mucosa with resultant ulceration. The mucosa of the bowel wall is the most vulnerable to ischemia of all the layers. An important role may be played by the bacterial proliferation due to the stasis of intestinal contents. Partially obstructing lesions in other parts of the gastrointestinal tract can produce inflammatory changes. This has been observed in the esophagus proximal to stenotic lesions at the esophagogastric junction and in the stomach proximal to obstructing lesions at the gastric outlet.[2]

The pathologic findings were consistent in the reported cases. Grossly, the bowel wall proximal to the obstruction was thickened, edematous, with variable degrees of dilatation. The mucosa was covered with hemorrhagic and purulent exudate. Numerous irregular, often confluent serpiginous ulcerations were found in the mucosa. The bases of the ulcers were covered with shaggy red to green fibrinous material. The margins of the ulcers were sharply outlined and the islands of mucosa between the ulcerations were edematous and congested.

CONCLUSIONS

The occurrence of ulceration proximal to an incompletely obstructing carcinoma of the colon has been recognized and a limited number of cases has been reported. The ragged ulcerations found proximal to the lesion may be indistinguishable from those found in inflammatory disease. The roentgen appearance in the affected colon is similar to that seen in acute and subacute ulcerative colitis, while in the terminal ileum the resemblance to granulomatous ileitis is striking.

The pathogenesis of these ulcers is probably related to bowel distention, stasis, ischemia and bacterial proliferation. The same mechanism may be operative in prestomal ileitis, the enterocolitis of Hirschsprung's disease and in fecal impactions. The necrotizing inflammatory process proximal to colon carcinoma which is incompletely obstructed may not be recognized if the bowel is not opened and examined at the time of operation. The attention of the surgeon should be directed to these findings, preoperatively, since anastomoses made in this abnormal bowel may result in delayed healing, leakage or actual perforation. A proximal protective diverting colostomy may be necessary to prevent complications at the anastomotic site. If possible, the entire segment of ulcerated inflamed bowel should be resected with a primary end to end anastomosis.

SUMMARY

1. Three patients with ulcerative changes in the bowel proximal to stenotic lesions of the colon are reported.

2. The roentgen changes are described and their similarity to inflammatory disease of the bowel is emphasized.

3. The inflammatory and ulcerative changes may mask the primary pathologic process.

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The authors wish to acknowledge the courtesy of Dr. Herman M. Meyer for permission to use Case III.

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DUPLICATION OF THE SMALL BOWEL SIMULATING REGIONAL ENTERITIS*

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THE embryology, symptomatology and roentgenographic findings of intestinal duplication have been well described in numerous publications.[1,2,4,6] Gross[2] found small bowel duplications to be the most frequent of all such anomalies.

The onset of symptoms from intestinal duplication varies from infancy to old age and some patients remain asymptomatic throughout life. Because of the relative fixation of the terminal ileum, duplications at this location often give rise to symptoms early in infancy. The patient usually presents with partial or complete small bowel obstruction. Secretions tend to fill a duplication until it is of sufficient size to cause mechanical obstruction by compression of the associated segment of bowel or the heavy duplication may produce volvulus or intussusception. On occasion, the duplication may cause pressure on adjacent mesenteric vessels and produce necrosis, bleeding and sloughing of the adjacent intestine.[2] The majority of duplications of the small bowel do not communicate with the neighboring small bowel. The duplications can contain any type of intestinal mucosa, regardless of the location. In those containing gastric mucosa, peptic ulcerations may develop with erosion from the ulcer causing a communication with the adjacent bowel. In those duplications that communicate, the secretions may cause ulceration in adjacent bowel segments that receive the liberated hydrochloric acid and pepsin. One must consider duplications in the differential diagnosis of all patients with small bowel obstruction, in any patient with gastrointestinal hemorrhage and in any patient with a palpable abdominal mass.

Roughly, 20 per cent of small intestinal duplications communicate with the adjacent bowel lumen. In some of these, a small bowel study will reveal an abnormal accumulation of barium in the duplicated segment. Not all communicating duplications will be opacified during the intestinal examination as will be demonstrated in the following case report.

The purpose of the author is to describe a patient who had symptoms consistent with duplication but whose roentgenographic findings led to the erroneous impression of regional enteritis.

REPORT OF A CASE

J. H., 223333, a 10 year old white male, was admitted to the Indiana University Medical Center on May 7, 1957. He had enjoyed good health until December, 1956 when he became tired and listless. In early January, he began to complain of abdominal pain. In late January, he developed intermittent vomiting and was subsequently hospitalized in another hospital on February 4, 1957. Roentgenograms of the small intestine suggested regional enteritis and on February 13, 1957 an exploratory laparotomy was done. The surgeon reported finding a perforation of the ileum and a biopsy was taken. The pathologist reported a simple chronic ulcer of the small bowel with secondary foreign body reaction in the submucosa and muscular layers. The cause was undetermined.

One week after discharge, the patient developed melena. Vomiting continued intermittently and he began to complain of pain in the penis which did not accompany micturition. The patient was re-admitted to the hospital on April 22, 1957. At this time, his red blood cell count was 1.23 million and his hemoglobin 4 gm. per cent. Repeat small bowel series again suggested regional ileitis. After blood transfusion, the patient was discharged with the recommendation of bland diet and glucosteriod therapy. Symptoms continued with the child

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losing 20 to 25 pounds over the subsequent period of his illness.

After admission to the Indiana University Medical Center, the patient had numerous studies, all essentially normal except for anemia, continued blood in the stools, and an abnormal examination of the small bowel. Figures 1 and 2, made at 15 and 30 minute intervals following the barium meal, demonstrated a long narrowed segment of distal ileum and some displacement of small bowel loops in the mid-abdomen. The long narrowed segment of ileum was interpreted as being the string sign of regional enteritis and the displacement of this narrowed segment from adjacent bowel loops was thought to be secondary to edema of the bowel wall and enlarged mesenteric lymph nodes. It was felt that the findings were consistent with the clinical impression of regional enteritis or could be a manifestation of involvement of the intestine by lymphoma. At no time during the child's illness did he have diarrhea. In fact, he was plagued with constipation. On June 19, 1957 the patient was taken to surgery where a segment of ileum, approximately 20 cm. proximal to the ileocecal valve, was found to be incorporated into a mass which was adherent to the bladder. Adjacent to the ileum, approximately 20 cm. proximal to the first mass, there was a separate cyst-like structure. A 40 cm. section of ileum was resected along with the described masses. The pathologist found both structures to be duplications of the ileum. The one, attached to the bladder, contained gastric mucosa which had ulcerated. This duplication was demonstrated to communicate with the adjacent ileum. Ulceration was seen in the ileum adjacent to this duplication and the ileum was found to have previously perforated. There was surrounding inflammation and edema of the wall of the

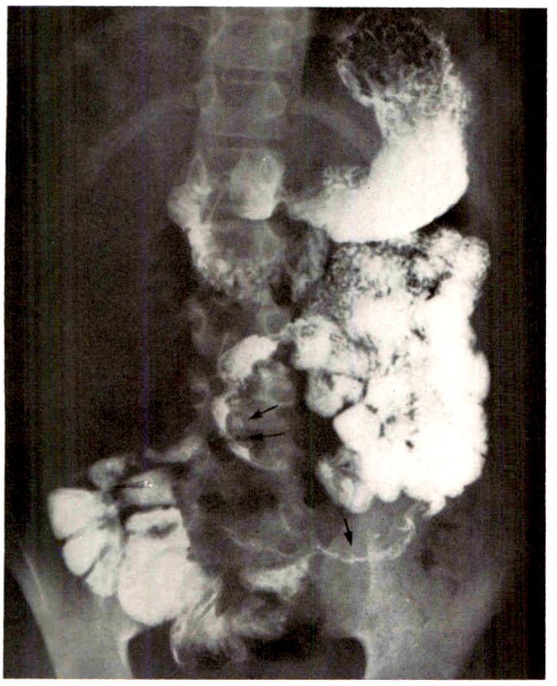


Fig. 1. Roentgenogram made 15 minutes following the ingestion of barium. The single arrow points to a long narrowed segment of ileum which was originally erroneously interpreted as representing the string sign of regional enteritis. Pathologic study demonstrated that the narrowing was caused by edema of the ileum that followed perforation of the ileum caused by a peptic ulcer which developed secondary to the passage of hydrochloric acid and pepsin into the ileum from an adjacent communicating duplication. The area marked with double arrows is representative of a duplication that caused displacement of the adjoining small bowel loops and produced an impression on the ileum where the duplication and ileum shared a common muscular wall.



Fig. 2. Roentgenogram made 30 minutes following injection of barium. The single arrow outlines a long narrowed segment of ileum adjacent to a communicating duplication. The double arrows outline the area of a proximal smaller ileal duplication that did not communicate with the bowel.

ileum. The long narrow segment of ileum seen at roentgen examination, and erroneously interpreted as representing the string sign of regional enteritis, was surrounded by edema and inflammation created when the bowel perforated. The perforation is presumed to have been caused by ulceration which developed secondary to spillage of hydrochloric acid and pepsin into the ileum from the duplication. The displacement of the small bowel loops in the mid-abdomen was thought to have been caused by distention of a more proximal duplication.

DISCUSSION

This case represents an unusual roentgenographic pattern of small bowel duplication. The pathologic specimen suggested that the narrowed segment of ileum was caused by surrounding edema and inflammation that followed perforation of the ileal segment. A similar roentgenographic pattern could have been produced by interference with the blood supply of the normal ileum by distention of the adjoining duplication. This is possible because all duplications lie on the mesenteric side of the bowel and share the blood supply with the adjoining bowel. Schwartz *et al.*[5] report roentgenologic patterns, indistinguishable from regional ileitis, caused by vascular compromise of the small bowel. The ileitis pattern has been seen in mesenteric thrombosis and embolus, Henoch-Schönlein purpura, necrotizing enteropathies, during anticoagulant therapy, following abdominal trauma and after incarceration of the bowel in a hernia. In addition, lymphoma and tuberculosis can produce a similar roentgenographic pattern. Jacobs[3] reports a case that simulated regional enteritis but was considered to be caused by changes secondary to roentgen-ray therapy. Starr *et al.*[7] have reported similar roentgenographic patterns accompanying carcinoid tumors.

The symptoms in this case were not typical of regional enteritis. There was no evidence to suggest hematologic disorders. Perhaps, the diagnosis would have been considered had the adage, "consider duplication in all patients with intestinal bleeding," been followed.

SUMMARY

1. A case of small intestinal duplication with roentgenographic findings suggesting regional enteritis is reported.

2. Other conditions, producing similar roentgenographic findings are mentioned.

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AN ANALYSIS OF THE NORMAL ANATOMIC RELATIONSHIPS OF THE COLON AS APPLIED TO ROENTGENOGRAPHIC OBSERVATIONS*

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A THOROUGH understanding of the normal anatomy is essential for the proper analysis of roentgenographically demonstrable abnormality within the abdomen. A precise comparison of the roentgenographic findings with the many known anatomic facts about the colon is lacking. The purpose of the authors is to better delineate the anatomy of the colon roentgenographically in light of the many known anatomic facts which study, in turn, will allow a better appreciation of other abnormality within the abdomen as it affects the colon.

MATERIAL

Plain roentgenograms of the abdomen, barium enema examinations, upper gastrointestinal examinations, cholecystograms and intravenous urograms were reviewed and correlation of these studies was attempted with descriptions given in standard books of anatomy and with the study of cadavers.

RESULTS

Perhaps a proper place to begin is the anatomic description or definition. In the standard textbooks of anatomy, the colon is divided into four parts: the ascending, transverse, descending and sigmoid colon. The ascending portion is described as commencing at the cecum, extending to the undersurface of the right lobe of the liver, where it is lodged within the colic impression of the liver, and then bending abruptly forward and to the left, forming the right colic (hepatic) flexure. This portion of the colon is generally devoid of peritoneum posteriorly and is thus "retroperitoneal," usually to the point where it passes over the inferior portion of the right kidney (Fig. 2 and 6*A*). Variation does occur, however. Treves[7] states that in 26 per cent of persons there is a mesentery of ascending colon which is, however, so short that it allows only a slight amount of movement of the gut. In the remaining 74 per cent of people, there is no mesentery at all. The colon then continues as the transverse portion (Fig 1*A*), passing over the right kidney, second portion of the duodenum and the head of the pancreas. As it crosses the right kidney, either a mesentery is formed or the short-fixing mesentery lengthens out. The transverse mesocolon is attached to the mid-portion of the head of the pancreas and to the inferior surface of the body and tail. The mesocolon passes above the duodenojejunal junction and over the upper portion of the anterior surface of the left kidney (Fig. 1, *A* and *B*), and then forms an acute angle as it descends abruptly. During this descent, it achieves its maximal posterior extension at which point it becomes fixed by the phrenicocolic ligament at the level of the tenth or eleventh rib. It is in this area that the colon is related to the inferior and posterior portions of the tip of the spleen. The colon then continues on as the descending segment, usually without mesentery (Fig. 3, *A* and *B*). Treves states that 64 per cent of cadavers are completely devoid of mesentery in

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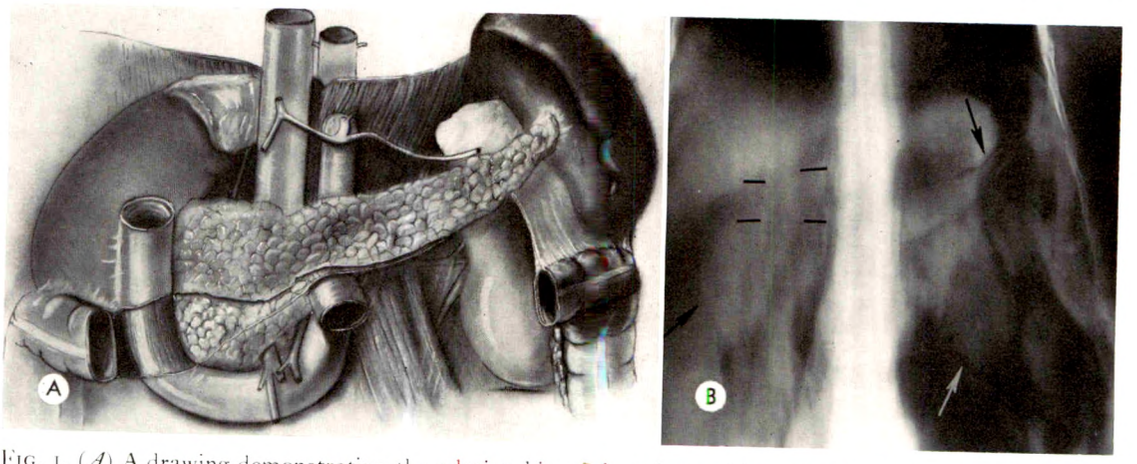


FIG. 1. (*A*) A drawing demonstrating the relationship of the colon and its attachments to the right kidney duodenum, pancreas, left kidney and adrenal and the spleen. Note the insertion of the transverse mesocolon along the inferior border of the pancreas. (*B*) A supine laminagraphic cut at 15 cm. from the table top following retroperitoneal oxygen insufflation. This demonstrates the tail of the pancreas (upper black arrow) passing over the superior portion of the left kidney (white arrow). The transverse mesocolon inserts at the inferior border of the pancreas so that the majority of the left kidney lies below the mesocolon. The right renal shadow (lower black arrow) is well outlined and its relationship to the inferior vena cava (four lines) can be seen.

their descending portion while 36 per cent have a mesocolon, the majority of these in the distal descending colon only. The proximal portion of the descending colon in the area of the phrenicocolic ligament only rarely has a mesocolon. The colon then again achieves a mesentery in its sigmoid portion.

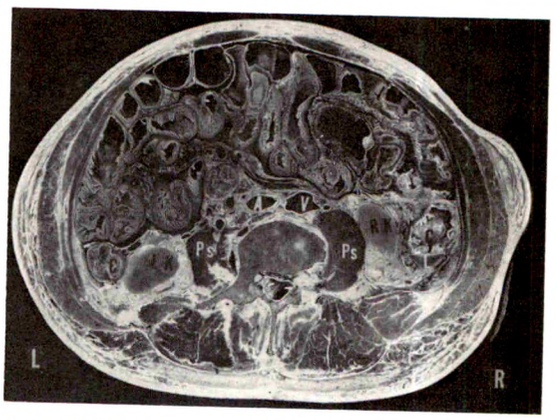


FIG. 2. Cross section at the level of the lower border of both kidneys. The retroperitoneal positions of both the right and left colon are well demonstrated.

The following is the code for Figures 2; 3, *A* and *B;* and 4: A—aorta, C—colon, D—duodenum, G—gallbladder, J—jejunum, L—liver, LK—left kidney, P—pancreas, Ps—psoas muscle, RK—right kidney, S—spleen, St—stomach, V—inferior vena cava.

In comparing roentgenograms with the descriptions in the anatomic textbooks, there seems to be some discrepancy. Taveras and Golden,[6] in their excellent work on abdominal masses, quote Dott as saying that the most constant portion of the colon is the splenic flexure fixed to the posterolateral aspect of the diaphragm by the phrenicocolic ligament and forming the support for the inferior edge of the spleen. What is usually referred to as the splenic flexure roentgenographically is the area of sharp angulation in the left upper quadrant. This area is ordinarily too high for the location of the phrenicocolic ligament and, secondly, varies in position with roentgenograms of the filled colon and roentgenograms of the evacuated colon. There is, then, great variation in the position of the roentgenographic left colic flexure which appeared to be in conflict with the true anatomic constancy of the left colic flexure (Fig. 7, *A* and *B*). This discrepancy has led us to believe that these are two different areas of the colon and that the roentgenographic splenic flexure is merely a portion

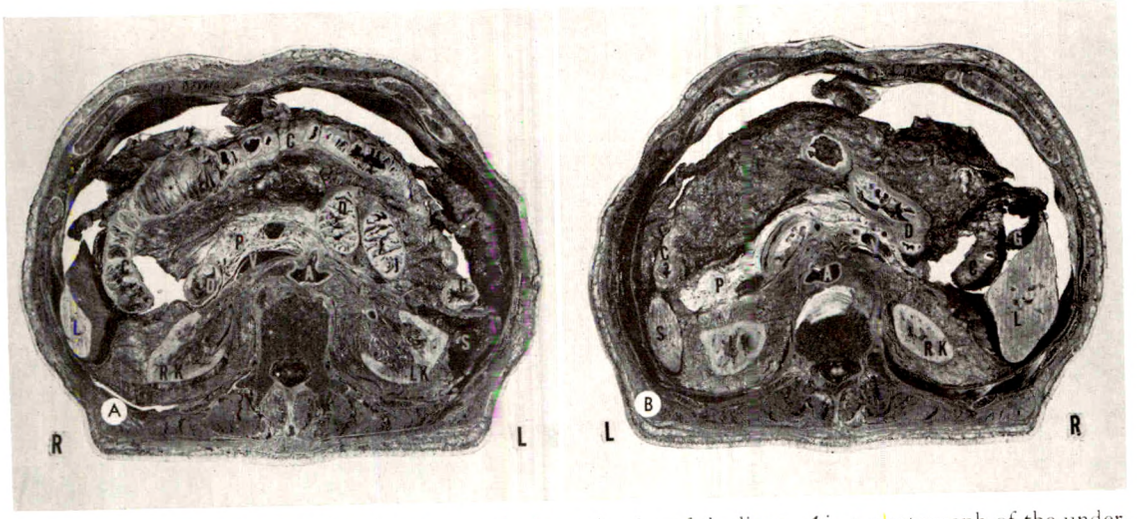


Fig. 3. Cross section through the abdomen at the lower border of the liver. *A* is a photograph of the undersurface of this section, *B* of the top surface. Demonstrated here are the relationships of the right colon to the undersurface of the liver, the right kidney, and the second portion of the duodenum. The relationship of the left colon to the spleen, the left kidney and the tail of the pancreas is well shown. (Refer to Figure 2 for code.)

of the mesenteric transverse colon and related to the anterior edge of the spleen rather than to its inferior edge at the phrenicocolic ligament. A second point that was apparent in viewing these roentgenograms was that there is great foreshortening of the flexures of the colon when they are filmed in the prone and supine positions, since much of the length of both flexures is oriented in an anterior posterior direction (Fig. 6*A* and 7*C*). To consolidate all this information, Figure 5, *A* and *B* represents what we feel is a correct relationship between the anatomic findings and the roentgenographic appearance of the colon. It is evident that the right colic flexure is an area extending from points 2 to 3 which, on the frontal roentgenograms, appears short. Its true length can only be appreciated on lateral and oblique roentgenograms. Point 1 represents the cecal area of the colon, point 2 represents the most posterior portion of the right colon, related to the inferior and lateral edge of the right kidney and the posterolateral tip of the liver, and the area from points 2 to 3, that portion of the colon traveling forward on the undersurface of the liver (Fig. 3*A*). Point 3 lies much farther anteriorly and is related to the gallbladder, rather than being in contact with the kidney which lies in a plane farther posteriorly. In fact, point 3 is separated from the kidney by the second portion of the duodenum (Fig. 4). Distal to point 3 is that portion of the transverse

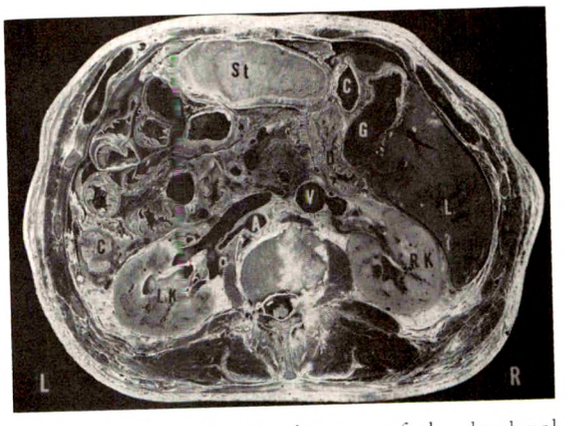


Fig. 4. Cross section in the area of the duodenal bulb. Here is shown the anterior portion of the colon, or the distal portion of the right flexure. The gallbladder can be seen to relate to this portion of colon. The gallbladder is separated from the kidney by the second portion of the duodenum. The portion of the right colon related to the kidney would be at a level lower than this. Again seen is the relationship of the left colon to the left kidney. (Refer to Figure 2 for code.)

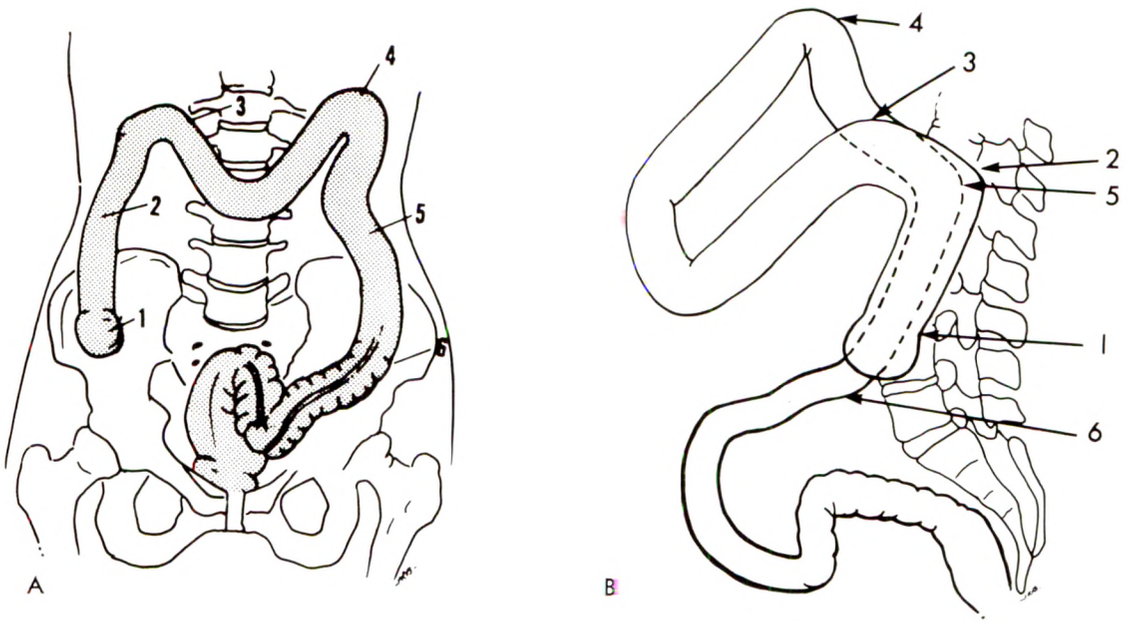


Fig. 5. (*A* and *B*) Diagrammatic drawings of the entire colon in frontal and lateral projections. The known anatomic portions of the colon are labeled from 1 to 6. 1—Ileocecal area; 2—the most distal portion of the fixed retroperitoneal right colon, the most posterior portion of the right flexure; 3—the area of the colon as it passes over the second portion of the duodenum, where the mesentery begins to lengthen; 4—the roentgenographic splenic flexure; 5—the anatomic splenic flexure; 6—that portion of colon which again becomes mesenteric, the beginning of the sigmoid colon.

colon in which the mesentery lengthens out; that is, the area overlying the second part of the duodenum and the head of the pancreas. Up to point 3 the colon is relatively fixed, with either no mesentery or a very short one. Beyond point 3 there is a longer mesentery and the colon is much freer to move. The area from points 3 to 4 then is the true mesenteric portion of the colon, and point 4 is that portion of the colon which in the past roentgenographically has been called the splenic flexure. All of the area from points 4 to 5 is mesenteric, however, and is usually anterior to the spleen since it has not reached the area of fixation by the phrenicocolic ligament. This is demonstrated in Figure 7, *A*, *B* and *C*. Point 5 is that portion of the colon which is fixed retroperitoneally, which is in constant relationship to the inferior tip of the spleen, which begins the retroperitoneal portion of the descending colon and which, by anatomic definition, is the splenic flexure. The area from points 5 to 6 is the fixed retroperitoneal descending colon. Point 6 begins the mesenteric sigmoid portion of the colon.

It is then apparent that portions of the right flexure are greatly separated from front to back, with a portion of the flexure related to the kidney and the posterolateral portion of the liver while the more anterior portion of the flexure as it comes forward on the undersurface of the liver is related to the gallbladder. It is also apparent that the area of the phrenicocolic ligament is a constant one, if looked for, on both the frontal and lateral roentgenograms and that this portion is truly related to the tip of the spleen, although the so-called roentgenographic splenic flexure is a mesenteric portion of colon and is more anterior.

DISCUSSION

In the majority of individuals, the right colon is a fixed structure, as is the left colon. The most constantly fixed portion of the entire colon is the area of the phrenicocolic

ligament. The variation in the appearance of the colon in the majority of cases is secondary to variation in the position of the mesenteric transverse colon. What has roentgenographically been called the splenic flexure is not the anatomic splenic flexure. The apparently variable splenic flexure is actually a portion of the mesenteric transverse colon while the area of the phrenicocolic ligament in most roentgenograms remains constant in position.

The importance of appreciation of these anatomic details is apparent in predicting the cause of colonic displacement by abdominal masses. In ordinary circumstances, it is reasonable then to predict the following: (1) Hepatomegaly will depress point 2 of the colon (the posterior portion) and push to the left the area between points 2 and 3. (2) A gallbladder mass will depress point 3 (anterior portion of the colon) but will not affect the area from points 2 to 3. (3) Right kidney masses will displace anteriorly the area from points 2 to 3 and will depress this

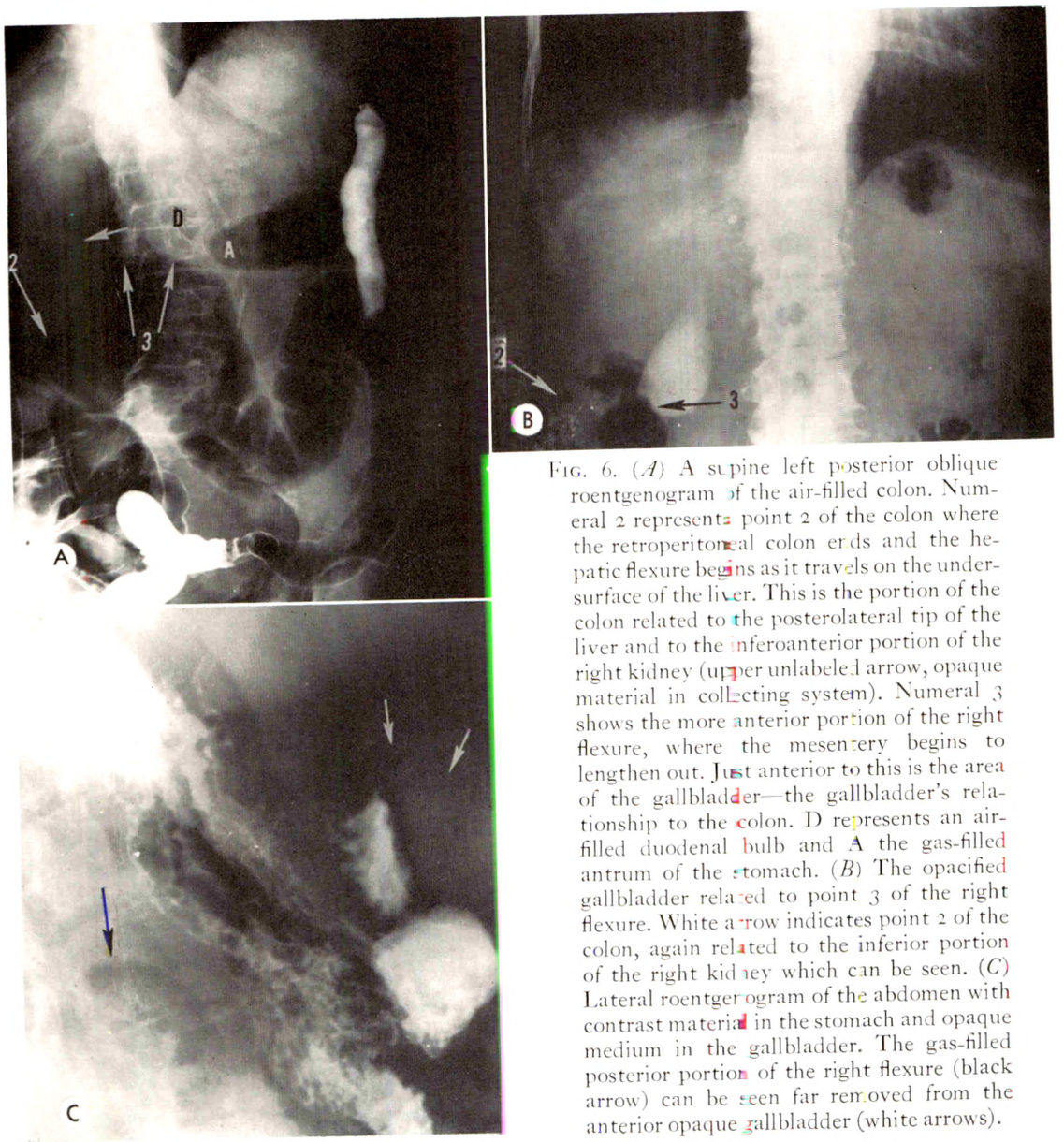


Fig. 6. (*A*) A supine left posterior oblique roentgenogram of the air-filled colon. Numeral 2 represents point 2 of the colon where the retroperitoneal colon ends and the hepatic flexure begins as it travels on the undersurface of the liver. This is the portion of the colon related to the posterolateral tip of the liver and to the inferoanterior portion of the right kidney (upper unlabeled arrow, opaque material in collecting system). Numeral 3 shows the more anterior portion of the right flexure, where the mesentery begins to lengthen out. Just anterior to this is the area of the gallbladder—the gallbladder's relationship to the colon. D represents an air-filled duodenal bulb and A the gas-filled antrum of the stomach. (*B*) The opacified gallbladder related to point 3 of the right flexure. White arrow indicates point 2 of the colon, again related to the inferior portion of the right kidney which can be seen. (*C*) Lateral roentgenogram of the abdomen with contrast material in the stomach and opaque medium in the gallbladder. The gas-filled posterior portion of the right flexure (black arrow) can be seen far removed from the anterior opaque gallbladder (white arrows).

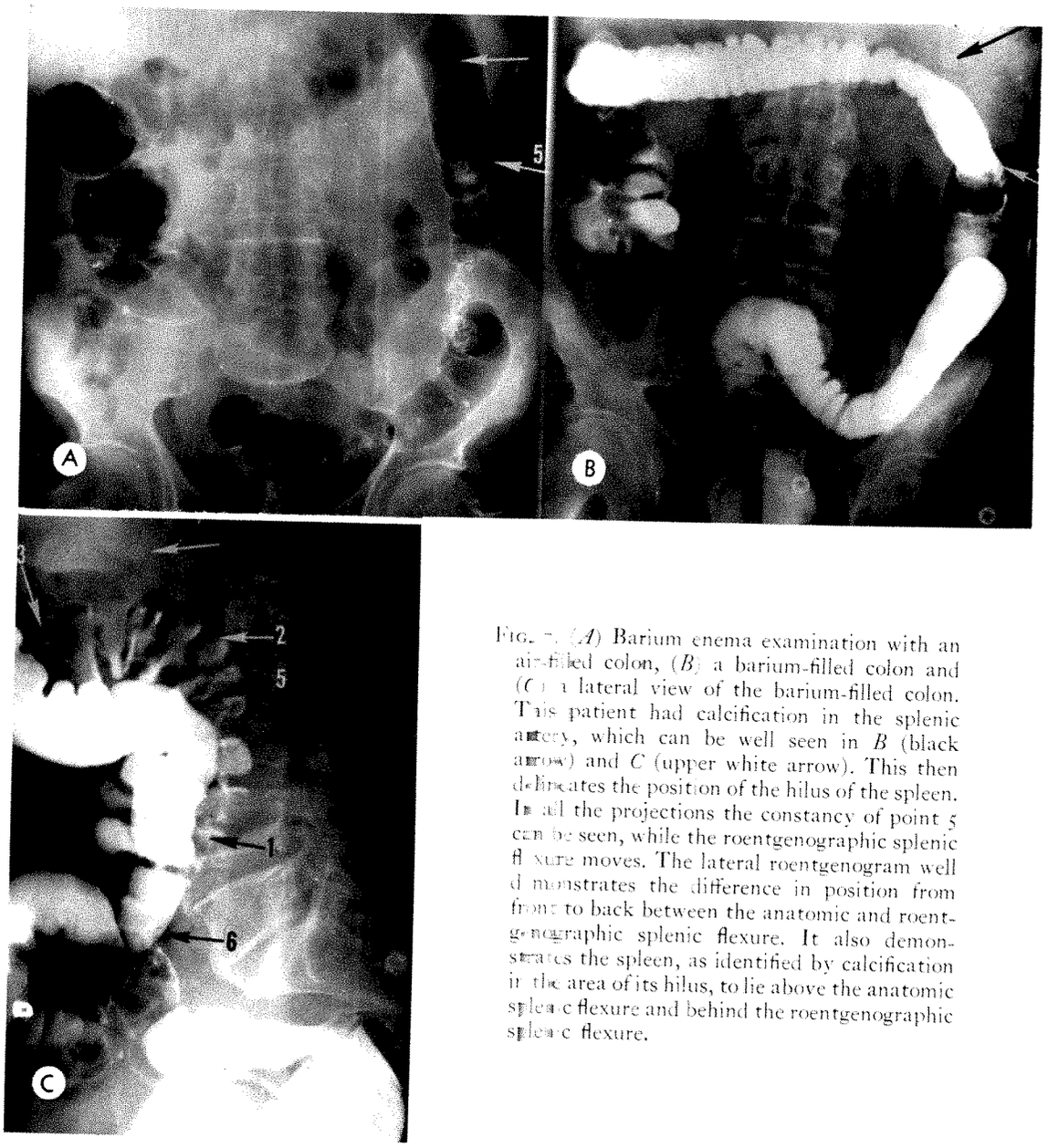


FIG. 7. (*A*) Barium enema examination with an air-filled colon, (*B*) a barium-filled colon and (*C*) a lateral view of the barium-filled colon. This patient had calcification in the splenic artery, which can be well seen in *B* (black arrow) and *C* (upper white arrow). This then delineates the position of the hilus of the spleen. In all the projections the constancy of point 5 can be seen, while the roentgenographic splenic flexure moves. The lateral roentgenogram well demonstrates the difference in position from front to back between the anatomic and roentgenographic splenic flexure. It also demonstrates the spleen, as identified by calcification in the area of its hilus, to lie above the anatomic splenic flexure and behind the roentgenographic splenic flexure.

segment. An exception to this might be a lesion of the very inferior pole of the right kidney which would lie beneath the mesocolon and could thus elevate the segment from points 2 to 3. Because the majority of the right kidney lies above the mesocolon, this upward displacement would be quite rare. (4) Right adrenal masses would displace the colon in a manner similar to masses of the upper portion of the right kidney. (5) Lesions of the pancreas would depress the area of the colon between points 3 and 4 since the insertion of the mesocolon is at the very lower edge of the pancreas. There is, however, the rare occurrence of an infracolic pancreatic lesion in which situation some pancreatic tissue insinuates itself below the insertion of the mesentery. (6) Lesions of the left kidney will elevate the distal portion of the seg-

ment from point 3 to point 4 and will laterally displace the portion of the colon from point 4 to point 5 since the majority of the kidney tissue on the left side is below the insertion of the mesocolon and the fixed portions of the left colon are lateral to the kidney. Again, an exception might occur if a mass arose in the very superior pole of the left kidney. (7) Left adrenal masses will displace the colon as a mass in the superior portion of the left kidney; *i.e.*, depress the segment between points 4 and 5. (8) Splenomegaly would depress point 5 of the colon (anatomic splenic flexure) and displace the portion from point 4 to point 5 of the colon to the right and forward. This gives the characteristic deformity we associate with splenomegaly. We have, however, noted a large number of cases with no displacement of the area from point 4 to point 5 (called by some the roentgenologic splenic flexure) and splenomegaly has been missed because of this. A lesion of the very tail of the pancreas could well displace the colon in a manner similar to the displacement caused by an enlarged spleen in that the tip of the tail of the pancreas rests in the hilus of the spleen and in many cases that portion of the pancreas is surrounded on all sides by peritoneum and is an intraperitoneal organ (Fig. 8). (9) Retroperitoneal tumors will displace the colon anteriorly from point 1 to point 3 and from point 5 to point 6.

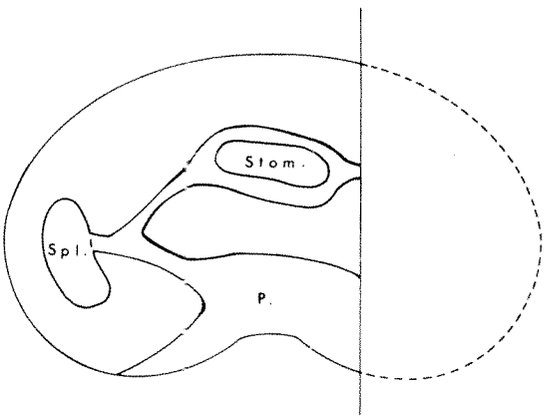


Fig. 8. Diagrammatic drawing shows the tail of the pancreas relating to the hilus of the spleen. It can be seen that there is peritoneal cavity in front of and behind the pancreas in this situation. This is not uncommon and in this case the tail of the pancreas is an intraperitoneal organ, intimately associated with the area of the hilus of the spleen.

SUMMARY

In summary, the anatomic relationships and predicted displacements of portions of the colon have been described. Exception has been taken to the identification roentgenographically of the so-called splenic flexure. On the basis of the anatomic relationships, an explanation of the usual displacement patterns of the colon by extracolic masses has been given.

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ROENTGENOGRAPHIC DIAGNOSIS OF SMALL AMOUNTS OF INTRAPERITONEAL FLUID*

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THE roentgenographic manifestations of minimal and moderate amounts of intraperitoneal fluid were first described in 1926 by Laurell.[12] The first report in the English literature by Westerborn[21] appeared in 1931. Frimann-Dahl[7] discussed the roentgenographic signs in great detail in 1939 and substantiated his findings by cadaver experiments. Subsequently, these studies were rather uniformly overlooked in numerous articles dealing with the roentgenologic diagnosis of ruptured spleen[1,9,19,20,22] and of other entities in which there is increased intraperitoneal fluid[6,10,11,17,18] until the recent reports by McCort[14,15] and Cimmino.[5]

It is our purpose to re-emphasize the roentgenographic evidence of relatively small increases in intraperitoneal fluid and to add some additional observations.

ANATOMY OF THE PERITONEAL CAVITY

The visceral layer of the peritoneum is intimately attached to nearly the entire surface of the abdominal organs. The parietal peritoneum follows the smoothly concave contour of the abdominal cavity anteriorly and laterally; on reaching the ascending and descending colon on the posterior wall, it turns anteriorly and becomes the visceral peritoneum covering these segments of intestine. This reflection of peritoneum forms a potential space along the lateral aspects of the colon referred to as the paracolonic gutters (Fig. 1).

Parietal peritoneum covers most of the posterior wall of the abdominal cavity, reflecting anteriorly along a diagonal line to form the small bowel mesentery and continue as the visceral peritoneum of the small intestine. The complex potential cavity formed between the two layers of peritoneum has been extensively examined roentgenologically after experimental intraperitoneal injections of various opaque media in cadavers[16] and during abdominal surgery.[2] These studies have shown that, when subjects are supine, various potential fossae are present on the posterior wall of the abdomen. Roentgenograms demonstrate that all of these compartments of the peritoneal cavity communicate normally and in the absence of adhesions there is relatively free flow of fluid, with the localization of any fluid present determined chiefly by gravity.[2] Diagnostic peritoneography[3] with iodinated organic compounds has been reported in an attempt to demonstrate the contours of the peritoneal cavity. More commonly, the borders of this potential space have been visualized when partial peritoneograms have resulted during studies of gastrointestinal perforations (Fig. 2) or ruptured bladders (Fig. 3). The particular fossae of present interest are the two lateral paracolonic gutters and the pelvic fossa (pouch of Douglas), since fluid

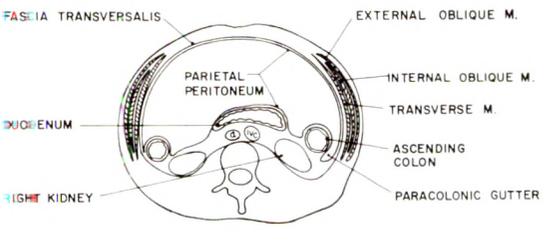


FIG. 1. Cross-section through mid-abdomen showing the formation of the paracolonic fossae as the most posterior extension of the peritoneal cavity in the abdomen.

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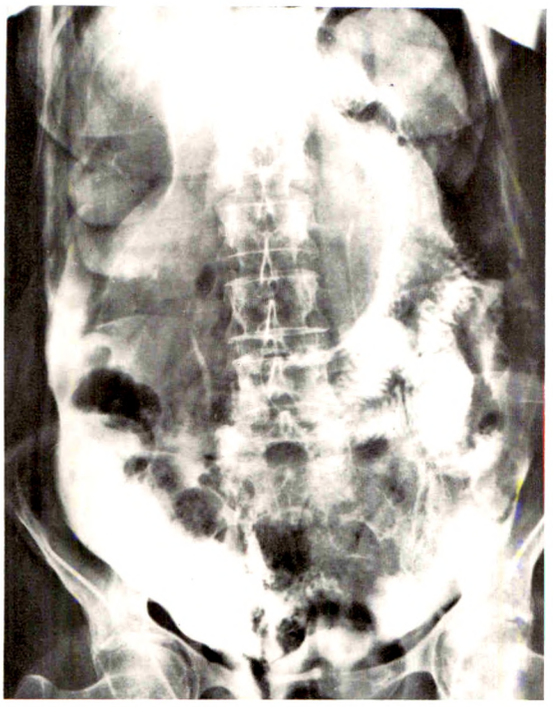


Fig. 2. Extensive leakage of hypaque during examination of perforated duodenal ulcer demonstrates extent of peritoneal cavity in abdomen; lateral borders represent margins of paracolonic fossae.

in these may be visible in roentgenograms.

A cross-section of all the layers of the abdominal wall (Fig. 4, *A* and *B*) is seen in the flanks in an anteroposterior roentgenogram of the abdomen. Laterally, the external and internal oblique and transverse abdominal muscles can often be identified as three bands separated by thin layers of adipose tissue. Medial to this, the properitoneal fat and occasionally also the intraperitoneal fat (such as the greater omentum) form a radiolucent zone varying in width from a few millimeters to a few centimeters;[8] this has commonly been referred to as the flank stripe. Occasionally, the parietal peritoneum will be visible within this zone as a fine, slightly convex, density extending from the lateral aspect of the liver and/or spleen caudad for varying distances. The medial border of the flank stripe in normal cases is usually poorly defined by adjacent small or large intestine as an undulating curve. However, this contour may be sharply defined and smoothly convex, when formed by distended colon, by a large greater omentum extending lateral to the intestine, or by a low lying inferior tip of the liver. When small bowel loops are interposed lateral to the colon (which occurs on the right side in 10 per cent of cases, on the left side in 55 per cent[4]) and these loops are distended, they will cause a multilobulated contour. Where intestine immediately subjacent to the parietal peritoneum in the flank is at least partly distended by gas or solid content, the thickness of its wall plus the peritoneum has been observed in our experience and that of others[5] to produce a narrow density no greater than 2 to 3 mm. in thickness.

The pelvic fossa is delimited caudally by the reflexion of parietal peritoneum from the anterior abdominal wall over the bladder to the rectum and cephalad by the pelvic brim (Fig. 5, *A* and *B*). The shape of the pelvic fossa will vary, depending upon the degree of distention of the bladder and rectum and upon the conformation of the sacrum. The fossa will be partially divided

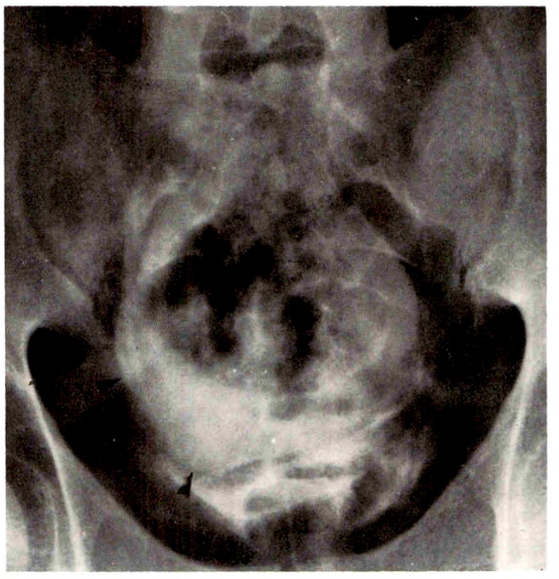


Fig. 3. Spill of hypaque during study of ruptured bladder demonstrating pelvic fossa (arrows) just above bladder.

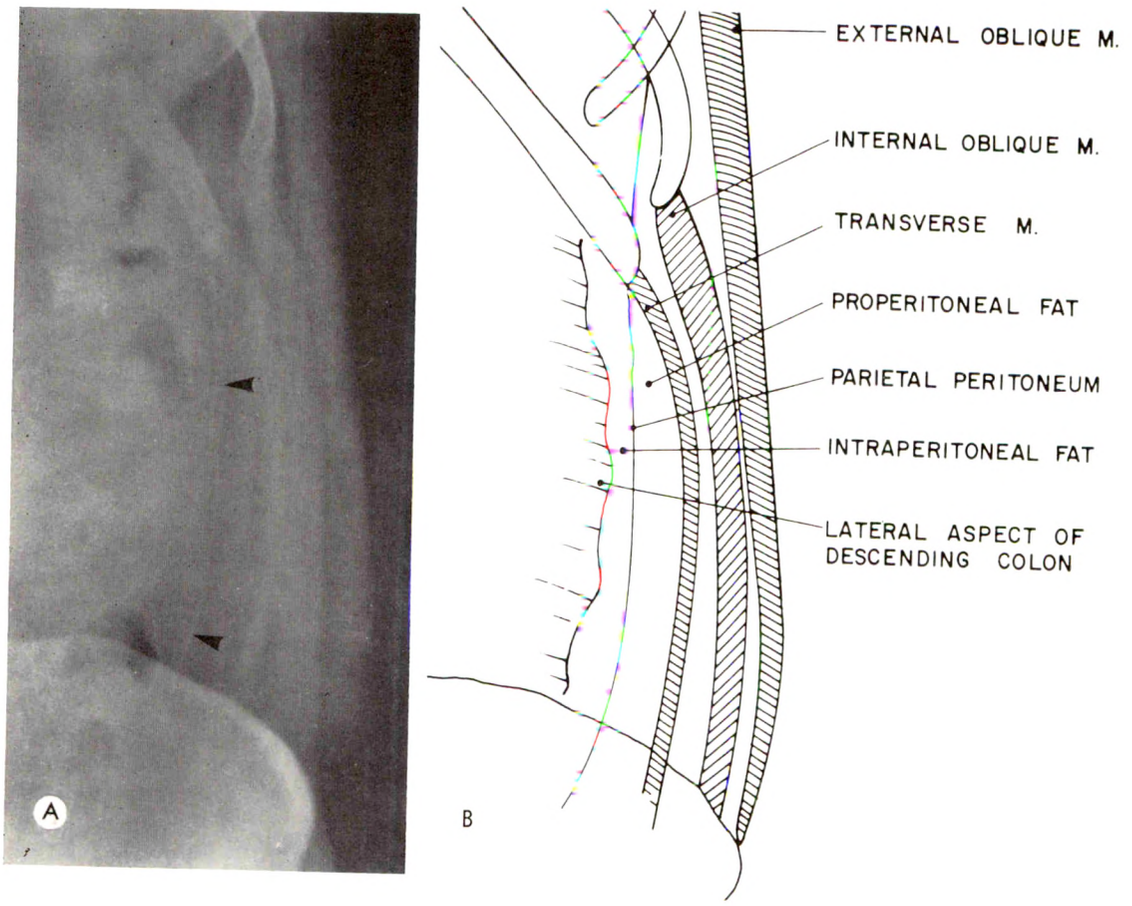


FIG. 4. (*A*) Normal roentgenographic anatomy in the flank. There is unusually extensive visualization of parietal peritoneum (arrows). (*B*) Diagram of roentgenogram.

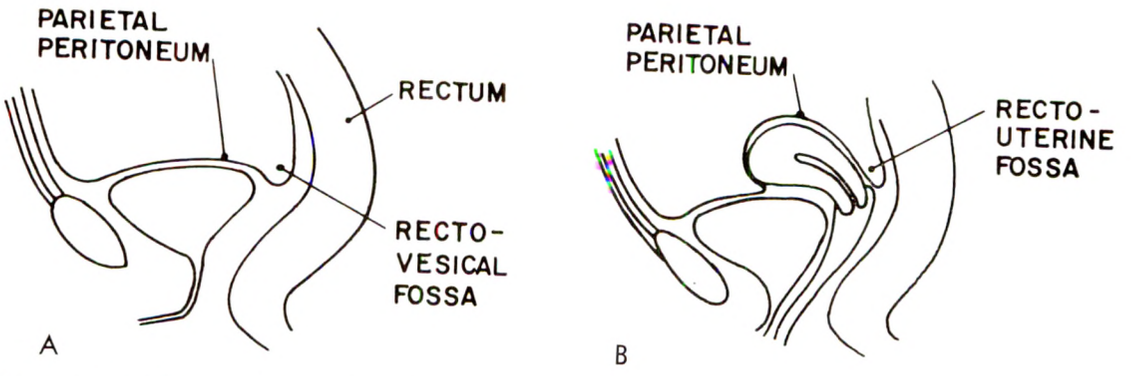


FIG. 5. (*A* and *B*) Mid-sagittal sections through pelvis showing the formation of the pelvic fossa as the most posterior extension of the peritoneal cavity in the pelvis.

into two laterally symmetric pockets, if the rectum is distended or the sacrum tends to be biconcave.

ROENTGENOGRAPHIC FINDINGS

We have encountered numerous conditions in which intraperitoneal fluid demonstrable in a roentgenogram has been confirmed at surgery. The site of earliest localization of free intraperitoneal fluid is determined chiefly by gravity. When the patient is supine, the pelvic fossa is the most dependent portion of the abdominal cavity and fluid will tend to gravitate here first. However, if the patient is in a lateral decubitus posture prior to the examination, fluid may appear in one of the paracolonic fossae unless peritoneal adhesions or blood clots[8] interfere with flow. Larger amounts of fluid may be visible in both the pelvic and the paracolonic fossae.

(A) ROENTGEN FINDINGS IN THE FLANK

(1) Very small amounts of fluid in the paracolonic gutter between the visceral and parietal peritoneum enhance the density of the peritoneum so that the interface with the properitoneal fat becomes sharply defined as a smoothly convex curve. This is usually visible even below the iliac crest (Fig. 6, *A*, *B* and *C*). Although a similar pattern may occasionally be found in the absence of peritoneal fluid, this finding is often sufficiently distinctive to be highly suggestive of increased fluid.

(2) Slightly greater amounts of fluid increase the width of the band between the properitoneal fat and the intestinal lumen beyond 3 mm.; this again is usually visible along the entire length of the flank (Fig. 7, *A*, *B* and *C*). The band becomes wider as the volume of fluid increases. Occasionally, the fluid also may be visible extending medially between haustral folds as wedge-shaped densities or between loops of small intestine to form an abnormally rounded intraluminal gas pattern.

(3) Larger amounts of fluid may cause the parietal peritoneum to bulge outward in the flanks; as a result the properitoneal fat zone is narrowed by overlying peritoneal contents. Such a change can be recognized as abnormal if it occurs on only one side, or if earlier roentgenograms show what the previous width had been (Fig. 8, *A* and *B*).

(4) The lateral surfaces of the liver and spleen are usually visible as a result of contrast with adjacent properitoneal fat. Their inferior surfaces are discernible only when sufficient intraperitoneal adipose tissue is present. We have found that intraperitoneal fluid in the flanks invariably obliterates the inferior margins of these organs (Fig. 9, *A* and *B*). If these contours are visible despite other findings which suggest fluid, the following conditions which simulate the presence of fluid must be considered: Fluid filled loops of small intestine situated lateral to the colon may present a relatively smooth contour resembling free fluid; however, this contour will usually be multilobular rather than representing a uniform curve and serial roentgenograms may show a changing gas pattern indicative of small bowel. An elongated inferior tip of the liver occasionally resembles free fluid lateral to the ascending colon; in the lateral decubitus position, free fluid shifts to the dependent left flank (Fig. 7, *A*, *B* and *C*; and 9, *A* and *B*), whereas the liver shadow persists. A retroperitoneal hematoma, peritoneal tumor mass or other soft tissue mass, in or outside of the colon, similarly would persist in lateral decubitus positions in contrast to the mobile peritoneal fluid. Laurell[13] recommended roentgenograms in the lateral decubitus position to better demonstrate fluid by collecting it in the dependent flank; however, in this position we have found that fluid within the intestine or the abdominal wall itself produces interfering shadows and this technique is of little value in the confirmation of suspected fluid. On the other hand, absence of a fluid density in the dependent flank is strong evidence against peritoneal fluid.

(B) ROENTGEN FINDINGS IN THE PELVIS

Frimann-Dahl[8] showed that by main-

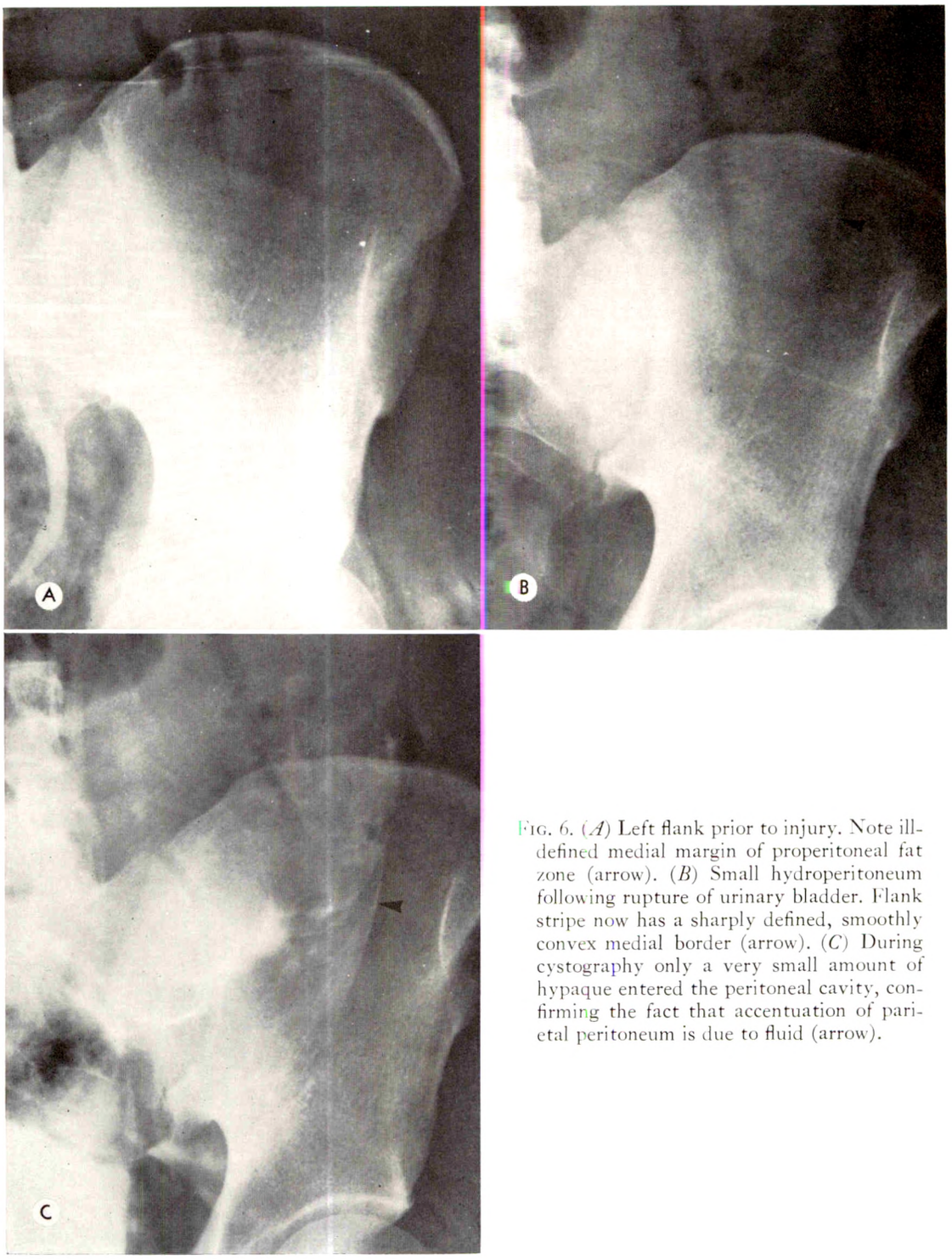


FIG. 6. (*A*) Left flank prior to injury. Note ill-defined medial margin of properitoneal fat zone (arrow). (*B*) Small hydroperitoneum following rupture of urinary bladder. Flank stripe now has a sharply defined, smoothly convex medial border (arrow). (*C*) During cystography only a very small amount of hypaque entered the peritoneal cavity, confirming the fact that accentuation of parietal peritoneum is due to fluid (arrow).

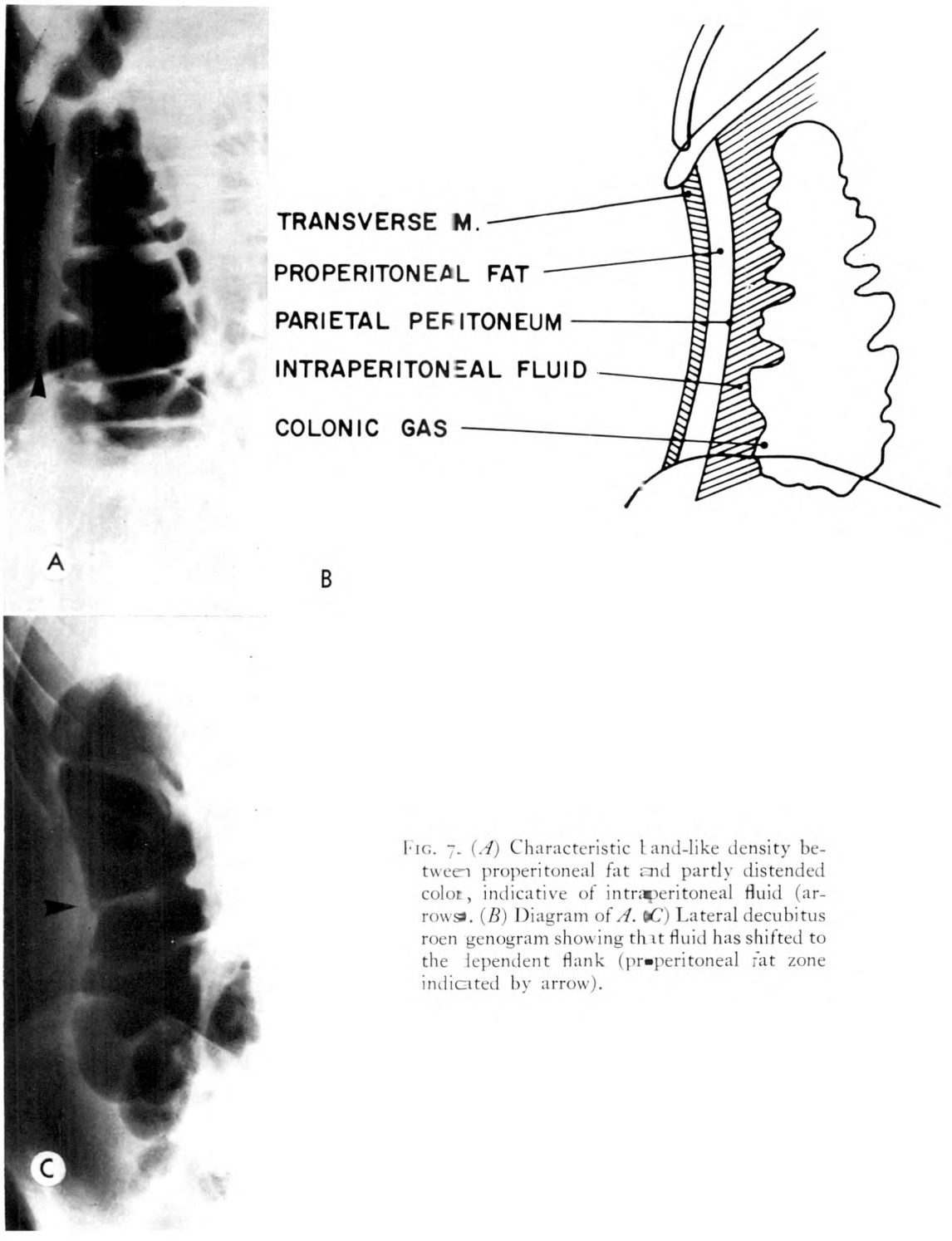


FIG. 7. (*A*) Characteristic band-like density between properitoneal fat and partly distended colon, indicative of intraperitoneal fluid (arrows). (*B*) Diagram of *A*. (*C*) Lateral decubitus roentgenogram showing that fluid has shifted to the dependent flank (properitoneal fat zone indicated by arrow).

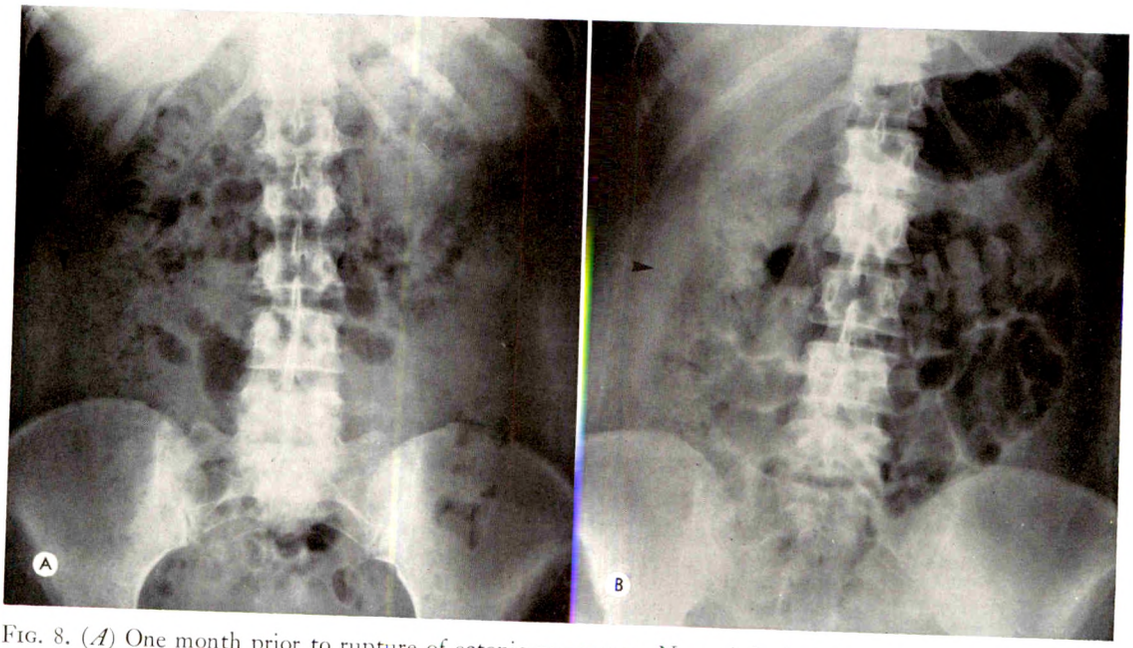


FIG. 8. (*A*) One month prior to rupture of ectopic pregnancy. Normal flank stripes are seen (arrows). (*B*) Small hemoperitoneum in right flank, visible as a band-like density in paracolonic fossa (arrow), has narrowed the properitoneal fat zone on that side (flank stripe on left remains unchanged).

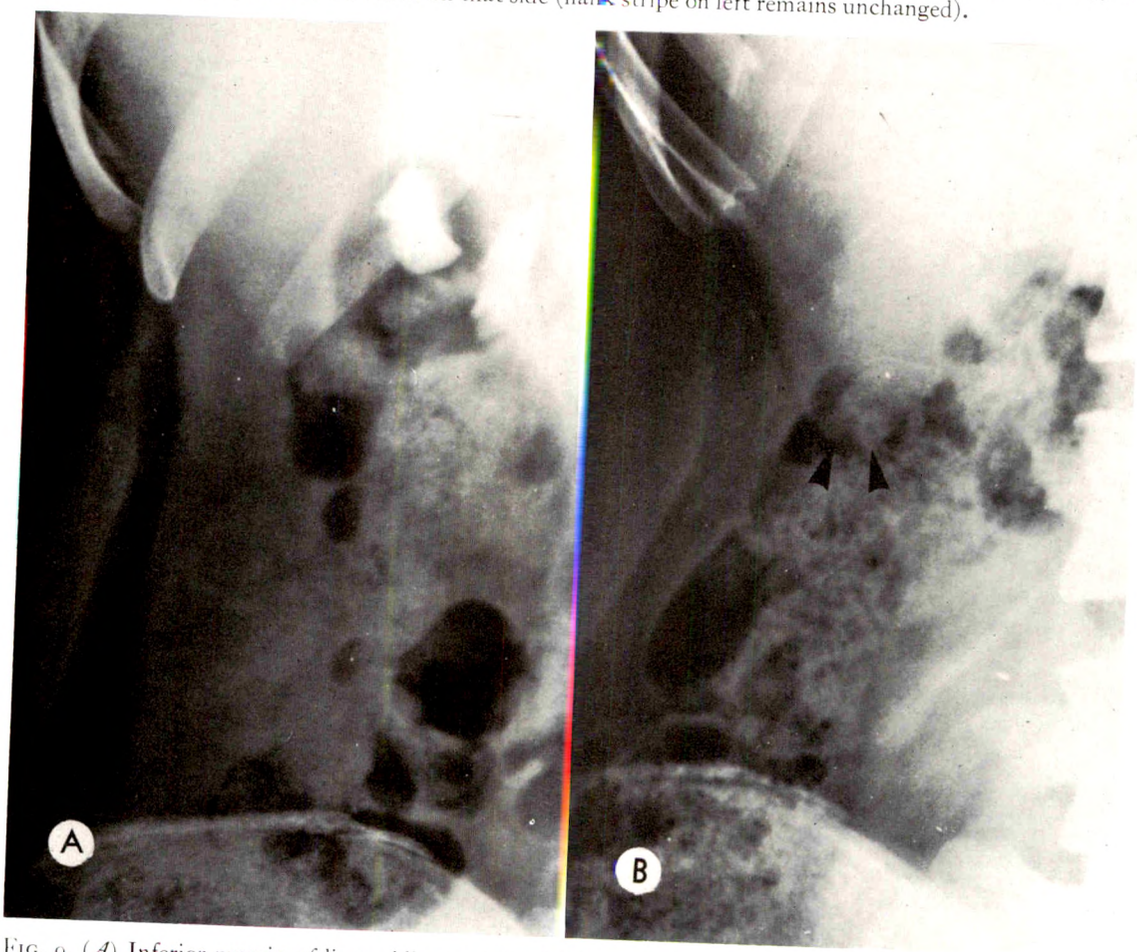


FIG. 9. (*A*) Inferior margin of liver obliterated by fluid (arrow) in paracolonic fossa, displacing ascending colon (rupture of perinephric abscess). (*B*) In lateral decubitus roentgenogram, mobile intraperitoneal fluid shifts to dependent left flank, now revealing inferior margin of liver (arrows).

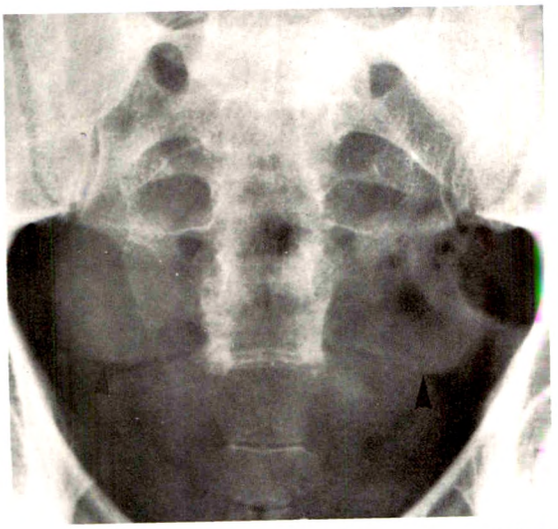


Fig. 10. Bilaterally symmetric intraperitoneal fluid collections (arrows) in pelvic fossa (hemoperitoneum due to ruptured branch of mesenteric artery following steering wheel injury).

taining the patient upright prior to the examination fewer than 100 cc. of fluid could be demonstrated in the pelvis as wedge-shaped densities separating segments of intestine when gas filled loops were present. In his cases, larger amounts of fluid produced a progressively wider crescentic density in the true pelvis just above the level of the symphysis, with extensions of the fluid projecting cranially and visible as wedge-shaped densities between loops of intestine.

In our experience, fluid in the pelvic fossa usually produced rounded densities bilaterally (Fig. 10) or in the mid-line (Fig. 11). A partly filled bladder sometimes appeared to facilitate demonstration of peritoneal fluid, evidently by displacing the fluid cranially into a deeper portion of the pelvis where a greater density resulted. We have often observed the shadow of fluid in the pelvic portion of the peritoneal cavity separated from that of the partly filled bladder by a characteristically uniform and narrow zone of radiolucency (Fig. 11). This is most likely due to extraperitoneal adipose tissue, as in the case of fluid in the flanks. To the best of our knowledge, this finding has never been described before.

Fluid in the pelvic peritoneal fossa is nearly always symmetrically distributed bilaterally, whereas a fluid filled loop of intestine which may resemble free fluid is generally asymmetric. The fluid may collect in the mid-line so that the corresponding roentgenographic density is nearly circular; such a finding is always abnormal in men, but in women should not be confused with the uterus. Except when the fluid is concentrated centrally, the superior border of the collection is generally poorly defined. This usually differentiates it from the normal uterus and bladder and solid tumor masses. Occasionally, the amount of fluid in the pelvic fossa is so small that it collects unilaterally in a pocket of the pelvic fossa formed by extrinsic pressure of the bladder; the shape may be sufficiently characteristic to be suggestive of free fluid.

Summary and Conclusions

Review of a series of cases in which increased intraperitoneal fluid was proved at surgery indicates the following roentgenographic findings demonstrable on plain roentgenograms.

1. The smallest amounts of intraperitoneal fluid may cause the medial border of the properitoneal fat zone to be sharply defined, smoothly convex and visible extend-

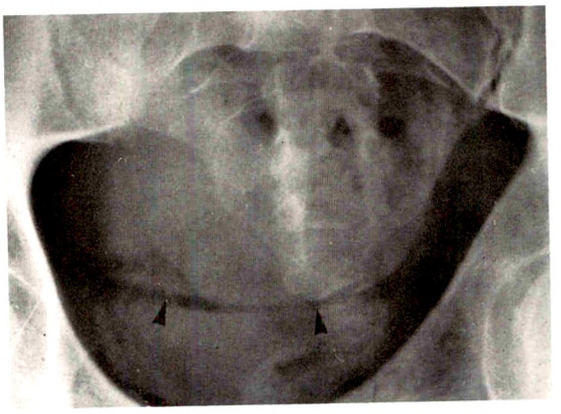


Fig. 11. Central collection of intraperitoneal fluid in pelvis (hemoperitoneum due to ruptured spleen). Note fine radiolucent zone separating pelvic fluid density from bladder (arrows).

ing below the iliac crest.

2. Greater amounts of fluid in the flank, in addition, produce a narrow band of homogeneous density medial to the properitoneal fat. The fluid may also be visible as wedge-shaped densities extending medially between haustral folds or intestinal loops.

3. The radiolucent flank stripe becomes progressively more narrow or is unilaterally narrow as a result of lateral bulging of the fluid filled peritoneal cavity.

4. Fluid collecting in the pelvis produces a bilateral or central symmetric area of homogeneous density with a smoothly convex inferior border. This is often delimited from the bladder by a characteristic narrow zone of radiolucency not previously described.

5. Fluid in the pelvis may be visible extending cranially between loops of intestine when gaseous distention is present.

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SPIGELIAN HERNIA CONTAINING SIGMOID COLON

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A SPIGELIAN hernia is a spontaneous hernia through the lateral aspect of the anterior abdominal wall.[1,2,3,4] It may occur anywhere in the linea semilunaris, *i.e.*, the curved tendinous line along the lateral border of the recti muscles, extending from the cartilage of the 9th rib to the pubic tubercle and formed by the aponeurosis of the internal oblique muscle at its line of division to enclose the rectus muscle, reinforced in front by the aponeurosis of the external oblique muscle and behind by the aponeurosis of the transversus muscle. The most common location, however, is in the lower quadrants at the linea semicircularis of Douglas. This line is the lower limit of the dorsal ensheathment of the rectus muscle by the aponeurosis of the transversus muscle. Below this line, the posterior sheath of the rectus muscle is absent and the weakness thus produced predisposes to the development of a ventral hernia. The hernia is of the interstitial type lying between the external and internal oblique muscles. The firm medial attachment of the external oblique aponeurosis to the rectus sheath forces dissection of the hernia interstitially in a lateral direction.

Most spigelian hernias are small, containing only omental fat.[4] Occasionally, when the hernia occurs in the left lower quadrant, sigmoid colon enters the hernial sac.

MATERIAL

We have studied 4 cases of spigelian hernias of the latter type. The presenting clinical finding in all 4 cases was a somewhat superficial left lower quadrant abdominal mass, the nature of which was a clinical diagnostic problem. This type of clinical presentation has been previously commented upon in a number of papers.[1,2,3] Of roentgen interest is the fact that all 4 cases provided a rather diagnostic picture on the barium enema examination.

ROENTGEN FINDINGS

The projection most useful for evaluating these hernias was a marked left posterior oblique, since this brought the neck of the hernia into profile. The neck of the hernia slightly constricted the sigmoid colon, producing minimal delay to the retrograde passage of the barium but no obstruction. The constriction upon the proximal end of the herniated loop was the more prominent. This is due to the greater thickness and strength of the combined aponeurosis of the

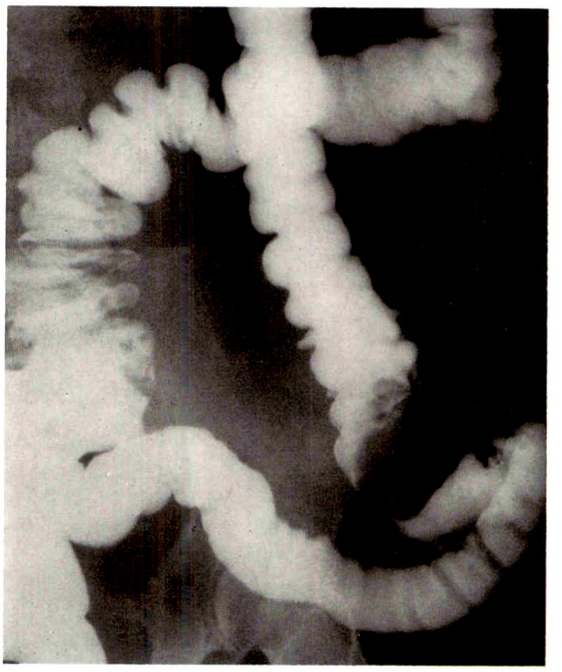


FIG. 1. Patient, S.R., aged 55 years. Left posterior oblique barium enema roentgenogram. Note the herniated sigmoid colon extending laterally, anteriorly and superiorly into the anterior abdominal wall. There is a sharp indentation on the upper loop at the hernia neck produced by the combined aponeurosis of the internal oblique and transversus muscles.

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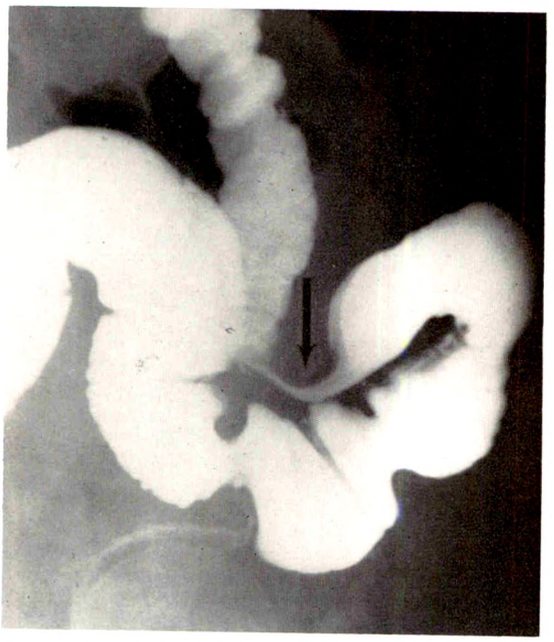


FIG. 2. Patient, S. W., aged 81 years. Spot roentgenogram showing the sigmoid colon entering the spigelian hernia. The neck of the hernia is well delineated. Note the well-defined extrinsic pressure on the upper loop (arrow). There is minimal pressure on the lower loop.

internal oblique and the transversus muscles which constitute the upper margin of the neck of the hernia at the linea semicircularis (Fig. 1 and 2). This finding was seen in all 4 cases and appears to be diagnostic.

The herniated sigmoid extended laterally, anteriorly and superiorly. In 2 cases, roentgenograms made with the soft tissue technique demonstrated the interstitial location of the herniated sigmoid. The external oblique muscle was seen covering the outer aspect of the hernia. The internal oblique muscle separated from the external oblique at the apex of the hernia and passed along its inner medial aspect. The barium filled herniated sigmoid and associated radiolucent omental fat were thus seen separating the two muscle planes (Fig. 3).

In differential roentgen diagnosis, consideration must be given to inguinal hernias and incisional hernias. Inguinal hernias are slightly lower in position, pass inferiorly toward the groin and scrotum and are rarely interstitial. They do not show the characteristic sharp pressure defect on the upper loop produced by the upper margin of the neck of the spigelian hernia. Incisional hernias have wide necks and pass through all layers of the abdominal wall into the subcutaneous tissues.

SUMMARY AND CONCLUSIONS

Spigelian hernias containing sigmoid colon may develop in the left lower quad-

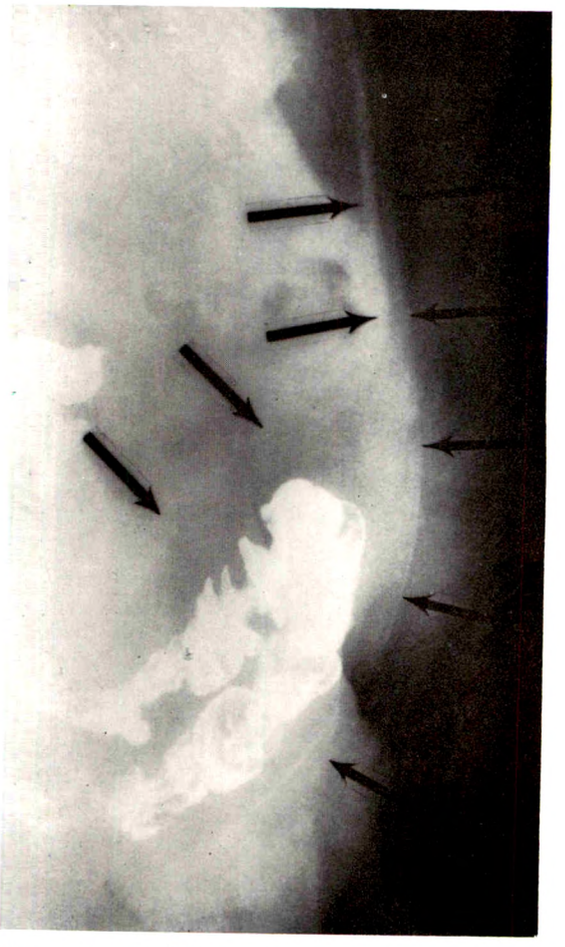


FIG. 3. Patient, S.R., aged 55 years. Postevacuation left posterior oblique barium enema roentgenogram with soft tissue technique. Note the separation of the external oblique muscle plane from the internal oblique muscle plane by the herniated sigmoid and associated radiolucent omental fat (arrows). The interstitial nature of the spigelian hernia is thus indicated.

rant through the lateral aspect of the abdominal wall at a point of weakness, the linea semicircularis of Douglas. They present clinically with a palpable, somewhat superficial, left lower quadrant mass. Barium enema study demonstrates the hernia and two findings diagnostic of its type: (1) the sharp pressure defect produced upon the upper loop of the herniated sigmoid by the combined aponeurosis of the internal oblique and the transversus muscles which constitute the upper margin of the neck; and (2) the interstitial nature of the hernia separating the external oblique muscle from the internal oblique muscle on roentgenograms made with the soft tissue technique.

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TOXIC MEGACOLON IN AMEBIC COLITIS*

REPORT OF A CASE

By DAVID FAEGENBURG, M.D., HAROLD CHEAT, M.D., PERRY R. MANDEL, M.D., *and* STUART T. ROSS, M.D.
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THE majority of persons infected with *Entamoeba histolytica* are asymptomatic carriers of the protozoon. Those patients with a clinically significant infestation usually run an indolent, insidious course characterized by bouts of diarrhea alternating with periods of constipation. Fever, when present, is low grade and intermittent. A small percentage of infected patients develop an acute amebic dysentery which manifests itself as a severe, mucus containing, bloody diarrhea. In 1 to 3 per cent of these acute cases,[1] the disease becomes fulminating and may even terminate fatally.

Several investigators have described abdominal distention occurring during the course of such a fulminant process.[1,2,3,8] It is our purpose to discuss the roentgen findings in a case of acute amebic colitis and to demonstrate the remarkable resemblance of these findings to those seen in so-called "toxic dilatation" of fulminating nonspecific ulcerative colitis.

REPORT OF A CASE

The patient, a 53 year old white female teacher, was admitted to Nassau Hospital because of a severe diarrhea of 5 to 6 weeks' duration. Approximately 1 week prior to the onset of diarrhea, she had undergone a barium enema roentgen examination of the colon because of gaseous distention and fullness of the abdomen (Fig. 1). This examination was originally interpreted as normal, but in retrospect disclosed a 10 cm. segment of spasm in the descending colon with nodular thickening of the mucosal folds in the spastic area. Approximately 1 week following the barium enema study, the patient developed a severe bloody diarrhea with passage of up to 14 stools per day. Sigmoidoscopy performed at this time was interpreted as normal. Following nearly 5 weeks of unremitting diarrhea, the patient was admitted to the hospital.

On examination, the temperature was elevated to 101.6° F. The radial pulse was 100. The skin was pale and dry. The tongue was coated. The abdomen was soft but slight generalized tenderness could be elicited by deep palpation.

The laboratory examination revealed a hemoglobin of 11.7 gm. per cent. The leukocyte count was 6,000 with a normal differential. This subsequently rose to 12,000 with a marked



FIG. 1. Barium enema study made approximately 6 weeks prior to admission. An area of persistent spasm is seen at the junction of the descending and sigmoid portions of the colon. There is nodular hypertrophy of the mucosal folds in this area. The remainder of the colon does not appear to be involved. At the time of this examination, the patient was experiencing vague abdominal distress without diarrhea.

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shift to the left. The stool was positive for occult blood. Two fresh stool preparations revealed only *Endamoeba coli*.

The patient's diarrhea continued unabated and resulted in an electrolyte imbalance which was controlled by administration of intravenous fluids. On the 15th hospital day, supine and erect plain roentgenograms of the abdomen were obtained and demonstrated marked distention of the transverse colon (Fig. 2). The bowel wall appeared thickened and presented a nodular appearance, suggesting the presence of pseudopolyps. The haustrations were reduced in depth and number. The roentgen diagnosis was fulminating ulcerative colitis with toxic megacolon. Because of the roentgen interpretation and the declining condition of the patient, a total colectomy was performed the following day. The patient rallied briefly following surgery but on the first postoperative day, she became cyanotic and pulseless and expired.

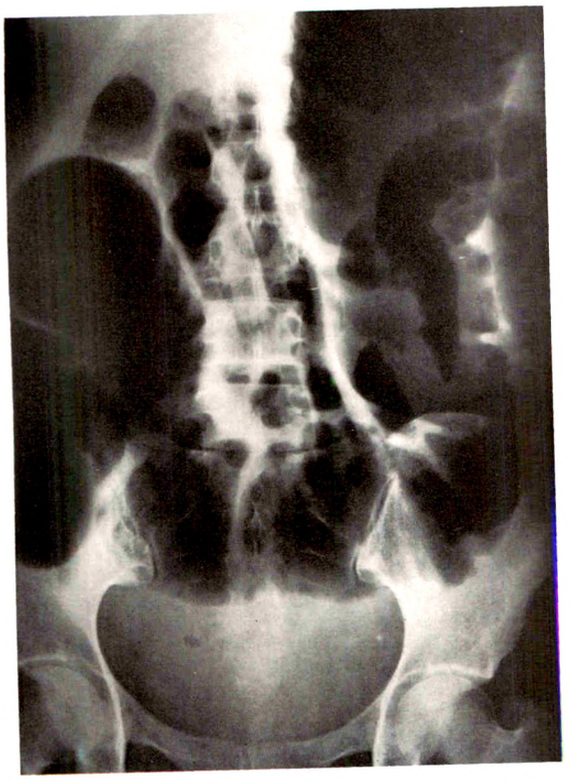


Fig. 2. Supine examination of the abdomen made 1 day prior to colectomy. The transverse colon, cecum and ascending colon are dilated. Haustrations are sparse and shallow. The bowel mucosa shows a nodular appearance, best seen in the segment of colon overlying the left iliac crest. Where adjacent loops are apposed, thickening of the bowel wall is evident. There is no evidence of free perforation.

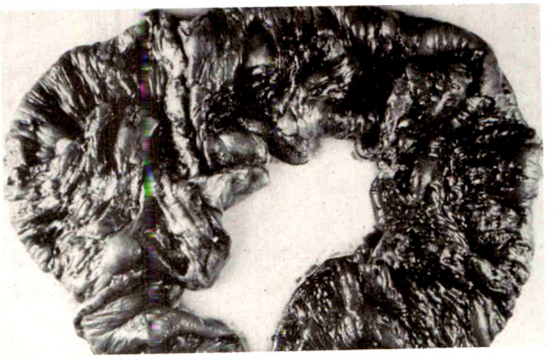


Fig. 3. A portion of the excised specimen. Deep fissure-like ulcerations, both discrete and confluent are present, particularly in the transverse colon. The mucosa between the fissures is heaped up and hypertrophied. The bowel wall is thickened. Areas of perforation are not demonstrated on this illustration, but were evident on the serosal surface.

Gross Pathology. The colon was dilated, predominantly in the cecal, ascending and transverse portions. The serosa and overlying fat were congested. Several perforations were present in the ascending colon and one at the splenic flexure. Upon opening the bowel, the most striking finding was the presence of many large ulcerations, both discrete and confluent. In the transverse and descending portions of the colon, the mucosa had a cobble stone appearance caused by edematous mounds of mucosa heaped up between the fissure-like ulcerations. A similar appearance was also present in the sigmoid (Fig. 3).

Microscopic Findings. Throughout the colon there were large areas of ulceration characterized by the accumulation of masses of fibrin containing many lymphocytes. The ulcerations were typically flask-shaped. Much of the fibrin had undergone necrosis. Within this necrotic exudate were many trophozoites of *Entamoeba histolytica*. The microscopic diagnosis was severe ulcerative colitis due to infestation by *Entamoeba histolytica*.

DISCUSSION

Segmental dilatation of the colon associated with fulminating nonspecific ulcerative colitis is a common and dreaded complication of that disease. The transverse colon is most conspicuously involved. The

dilated segment is characteristically devoid of haustra. Solid fecal material is absent and, when fluid levels are present, they are unusually long. The bowel wall is thickened and a thin lucent stripe is occasionally seen interposed between adjacent loops. The prevailing concept is that this represents intramural dissection of gas.[11] An almost constant finding is a wavy contour of the mucosal surface representing pseudopolyps. The above findings in a patient running a toxic course with severe diarrhea are considered characteristic of fulminant nonspecific ulcerative colitis.[5,6,7,9,10,11]

As pointed out by Weinfeld,[12] and Wruble *et al.*,[13] there are many pathologic and roentgenologic similarities between various stages of nonspecific ulcerative colitis and corresponding stages of amebic disease of the colon. Clinically, the fulminant stage of amebic dysentery strongly resembles that of ulcerative colitis. In our case, the appearance of the colon on plain roentgenograms of the abdomen was indistinguishable from toxic megacolon of idiopathic ulcerative colitis. With the exception of the intramural gas stripe, all of the classic findings of toxic dilatation were present. Even at operation, the diagnosis of amebic colitis was not suspected and was revealed only by scrupulous microscopic evaluation.

SUMMARY

A case of toxic megacolon is described occurring during the course of a fulminant and eventually fatal amebic colitis. Both clinical and roentgenologic findings were felt to represent fulminating ulcerative colitis of the nonspecific type. Despite a successful panproctocolectomy, the patient died of peritonitis resulting from multiple perforations of the dilated colon.

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ROENTGEN DIAGNOSIS OF INTESTINAL AMEBIASIS*

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THE American radiologic literature in the last 20 years has contained few articles pertaining to amebiasis. Most reports on the roentgenologic diagnosis of this infestation have emphasized the frequent small deformed cecum and the absence of involvement of the terminal ileum (Fig. 1).[4,5–7,10,13–15] The purpose of this report is to illustrate other roentgen signs that may suggest the presence of amebiasis. Of particular importance is the radiologist's ability to differentiate between the diagnosis of carcinoma and amebiasis. An erroneous diagnosis of carcinoma could lead to surgical intervention in a patient who has not received the benefit of antiamebic drugs. Because the inflamed bowel heals poorly after resection, such surgical intervention is frequently fatal. Ochsner[9] stated that the surgical mortality in patients with acute amebiasis in the Chicago epidemic of 1933 was 43 per cent. When amebiasis is confused with other inflammatory diseases, inappropriate or delayed treatment may result.

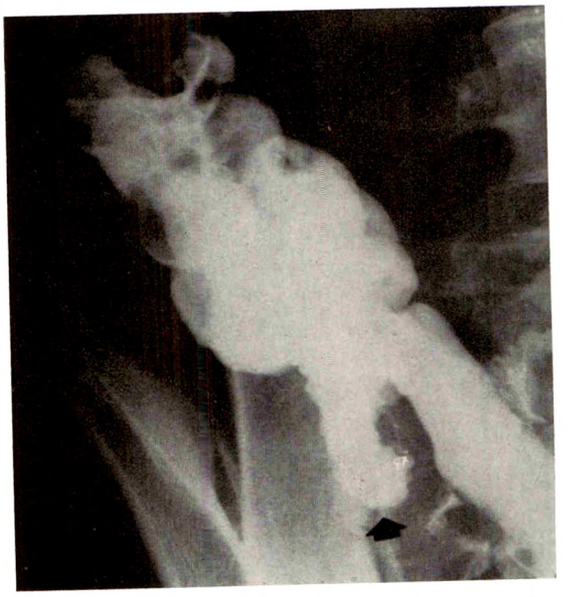


FIG. 1. A shrunken deformed cecum (arrow) and a normal terminal ileum are the most typical roentgen findings in amebiasis.

Although the over-all incidence of amebiasis in the United States is about 5 per cent,[1] it varies greatly in different locations and with different population groups. Usually, the infestation is derived from food or water contaminated by feces that contain viable cysts of *Entamoeba histolytica*. The walls of the ingested cysts disintegrate in the small bowel, releasing trophozoites. These organisms usually pass into the colon before invading the mucosa and establishing themselves in the bowel. Most carriers of amebiasis are asymptomatic. Those with symptoms of the disease are usually suffering from either acute amebic dysentery or amebic granuloma. In patients with chronic amebiasis, acute exacerbations may develop. Extraintestinal amebiasis, in such form as liver abscess, is secondary to bowel infestation. Ultimately, the diagnosis of amebiasis depends on histologic recognition of the organism.

Familiarity with amebic infestations by physicians is not as extensive in the United States as in the tropical climates where this disease is more common. Brooke[1] expressed the belief that even laboratory diagnosis of amebiasis in this country is sometimes inaccurate because of this unfamiliarity. Thus, patients may well be referred for roentgen examinations before the clinical diagnosis is established. In all likelihood, attempts to identify the organism microscopically will persist only when the roentgen signs indicate consideration of this diagnosis.

Trophozoites are more likely to be present in diarrheal stools and cysts are more common in formed stools. At least 6 sep-

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arate specimens of fresh, warm stools should be examined. Doxiades and Yiotas[3] have emphasized the importance of rectal biopsy even in the presence of apparently normal rectal mucosa. When results of stool examinations for parasites are reported as negative, biopsy is a useful addition.

Many drugs have been used in the treatment of amebiasis. In general, acute intestinal amebiasis responds rapidly to drug therapy and can usually be cured. The chronic form can be improved and sometimes cured. Shookhoff[11] recommended a course of emetine in acute amebiasis, to be followed by treatment with sulfasuxidine, penicillin, oxytetracycline, and diodoquin. In less acute instances, emetine was to be omitted and diodoquin or carbarsone substituted. Chloroquine is useful when the liver is involved. After completion of therapy, Shookhoff based cure on the following criteria: Clinical manifestations were to be absent for 1 year and postcathartic stool specimens were to be negative for *E. hystolytica* on at least 6 different occasions after completion of therapy. When cure was not accomplished, reasonably good health was to be maintained by periodic courses of specific therapy.

The following case reports illustrate some of the other roentgen features that can be seen in amebiasis.

REPORT OF CASES

CASE I. A 68 year old Mexican woman was admitted to the San Francisco General Hospital with abdominal pain and bloody diarrhea of 1 week's duration. A similar episode in Mexico 3 weeks previously had subsided with medication prescribed by a Mexican physician. The contents of the medicine were unknown to the patient.

On admission, the physical examination disclosed generalized abdominal tenderness, marked tenderness on rectal examination, and a temperature of 101.6° F. A barium enema examination was performed (Fig. 2, *A* and *B*). Examination of stools showed the presence of *E. histolytica* trophozoites. On sigmoidoscopy, a reddened mucosa and a white exudate were seen. Rectal biopsy revealed a nonspecific inflammation with *E. histolytica* in the fibrinous exudate.

Anti-amebic drug therapy, which included entero-vioform and tetracycline, was followed by a course of emetine and carbarsone. Barium enema examination was repeated 18 days after the initial barium study (Fig. 2, *C* and *D*). Follow-up barium enema examinations showed the visualized lesions to be stable but retrograde filling beyond the transverse colon was not achieved. Antegrade passage of feces was not obstructed, however. The patient returned to Mexico 7 months after admission. At that time, she had improved clinically and the results of stool examinations for amebae were negative.

CASE II. A 3 year old Mexican born girl was admitted to the University of California Medical Center, San Francisco, because of intermittent, bright red, rectal bleeding of 1 month's duration. The patient had been in the United States for the preceding 2 years. No history was elicited of loose stools, although the parents had noticed that the child's evacuation was slightly more frequent.

The results of the physical examination were unremarkable except for pallor of the mucous membranes. The hemoglobin value on admission was 6.2 gm. Digital examination of the rectum revealed no abnormalities. A barium enema examination was performed (Fig. 3, *A* and *B*). Proctoscopic examination revealed a hyperemic rectal mucosa and confirmed the presence of a shallow ulceration on the posterior rectal wall. On histologic examination of fresh, wet stool specimens, numerous motile trophozoites of *E. histolytica* were seen. After treatment with chloroquine, vioform, and oxytetracycline, the child became asymptomatic and the results of examinations of stool became negative for amebae. Repetition of proctoscopic examination showed that the rectal ulcer had healed. The child was discharged on the twenty-third hospital day.

CASE III. A 47 year old Mexican born man was admitted to St. Luke's Hospital, San Francisco, with pain in the right lower quadrant and with diarrhea. He had resided in San Francisco for 20 years, but had returned occasionally to Mexico. Five years before admission, while in Mexico, the patient was operated on for "liver infection."

On admission, examination revealed an en-

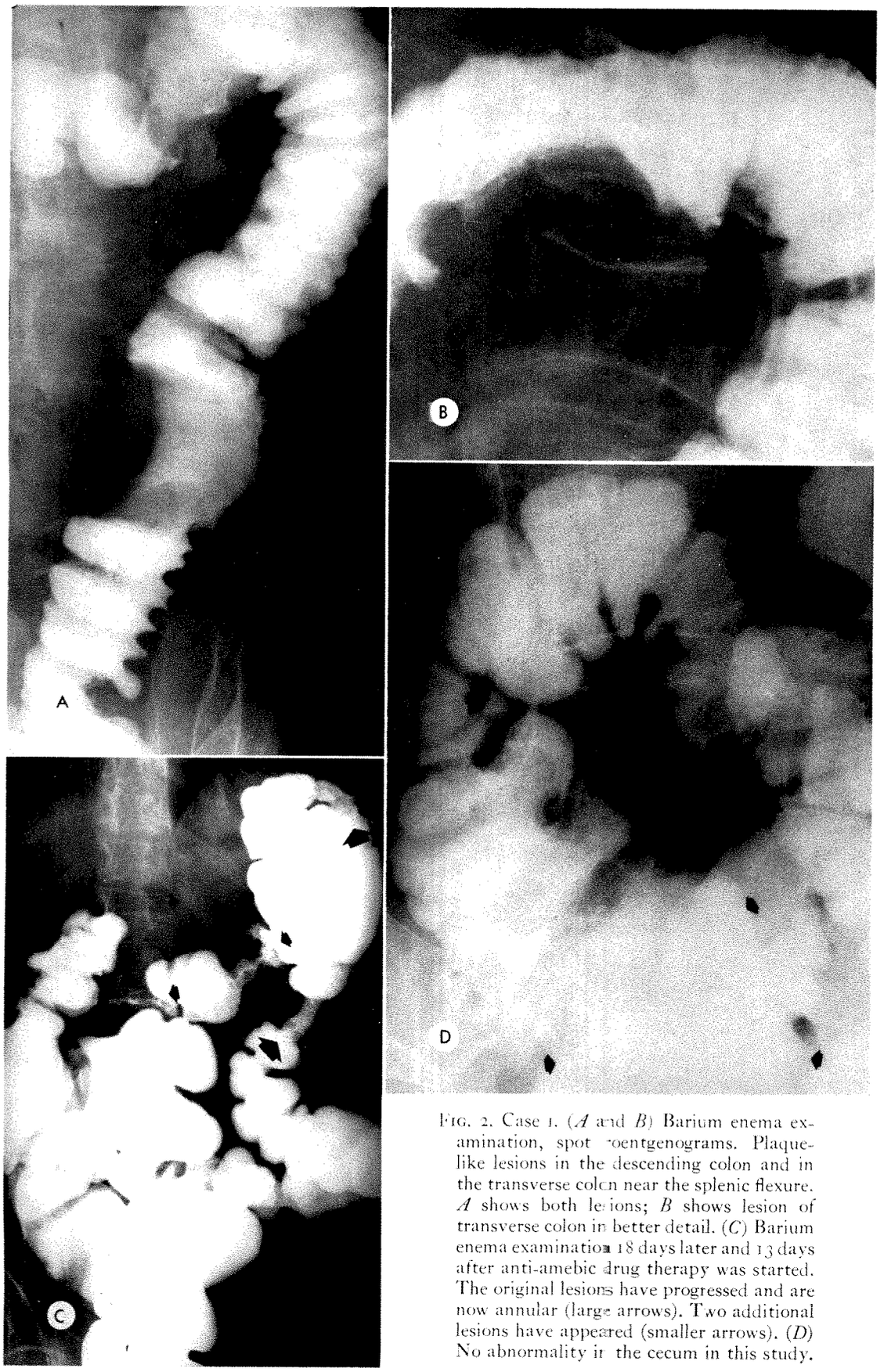


FIG. 2. Case 1. (*A* and *B*) Barium enema examination, spot roentgenograms. Plaque-like lesions in the descending colon and in the transverse colon near the splenic flexure. *A* shows both lesions; *B* shows lesion of transverse colon in better detail. (*C*) Barium enema examination 18 days later and 13 days after anti-amebic drug therapy was started. The original lesions have progressed and are now annular (large arrows). Two additional lesions have appeared (smaller arrows). (*D*) No abnormality in the cecum in this study.

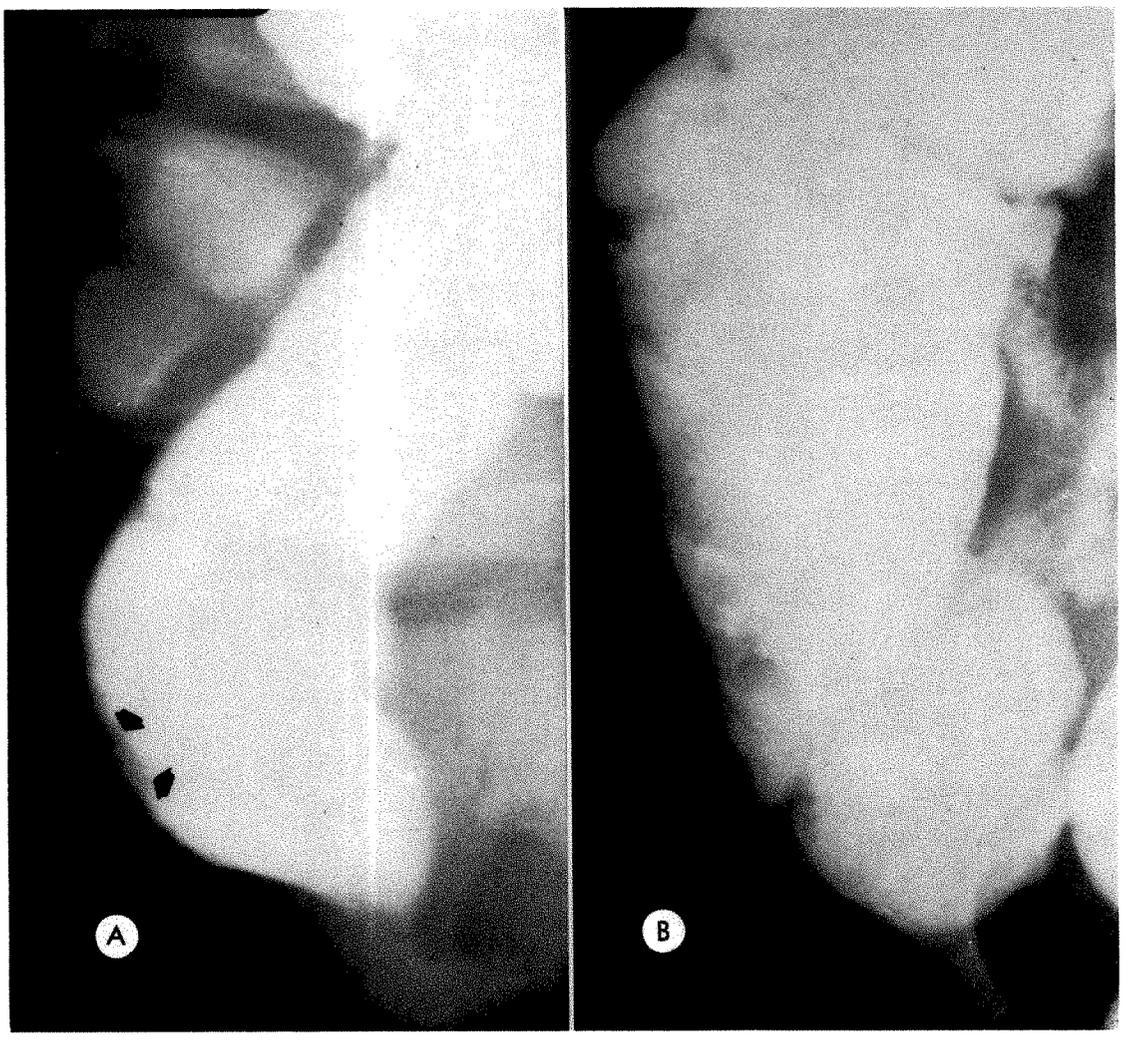
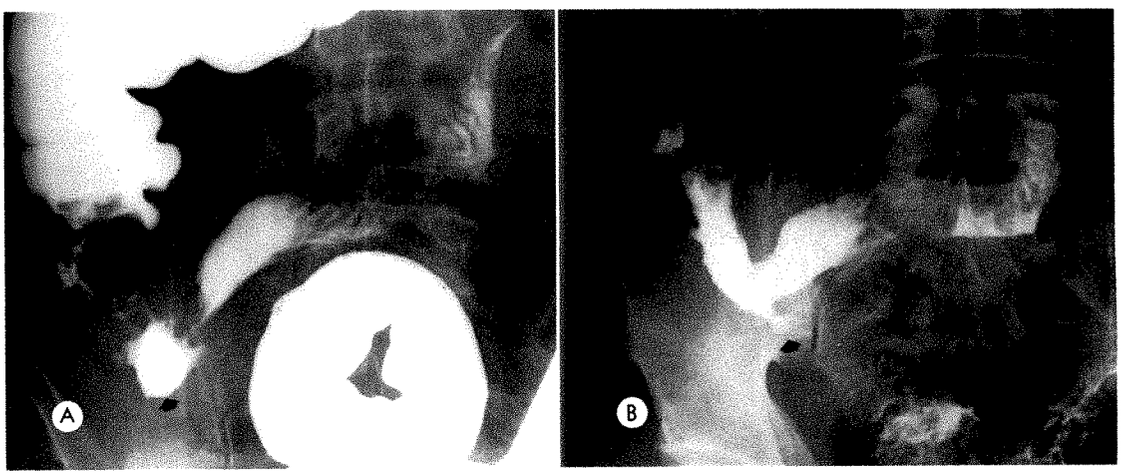


FIG. 3. Case II. Barium enema examination. (*A*) Shallow ulceration on posterior wall of rectum. (*B*) Normal cecum and terminal ileum.



larged liver and a tender mass in the right lower quadrant. Results of sigmoidoscopy were unremarkable. A barium enema examination was performed (Fig. 4, *A* and *B*). The results of 3 stool examinations were reported as positive for cysts of *E. histolytica*. Roentgen examination of the chest showed no abnormality.

Treatment with carbarsone was begun, resulting in marked clinical improvement. The patient was lost to follow-up.

Case IV. A 46 year old woman, a former resident of New Orleans, was admitted to the orthopedic ward because of low back pain of 3 months' duration. Initially, a diagnosis of back strain was made and she was treated by means of pelvic traction. On admission, the patient had mentioned occasional episodes of rectal bleeding and urgency, but these complaints were overshadowed by her back pain. Her temperature on admission was 101° F. While under traction, the patient suddenly became acutely ill with marked abdominal distention. Abdominal roentgenograms were obtained on an emergency basis (Fig. 5*A*). The radiologic resident made a diagnosis of ulcerative colitis. The surgical resident, uncertain of the results of sigmoidoscopic examination, insisted upon barium enema examination. Fortunately, the colon was not perforated (Fig. 5*B*). The rectal biopsy and repeated stool examinations gave no evidence of amebae. The patient was given cortisone, antibiotic therapy, and blood and fluid replacement, as for acute ulcerative colitis. Finally, 18 days after the onset of the acute episode, *E. histolytica* trophozoites were identified in the stools and anti-amebic therapy with vioform, tetracycline, and chloroquine was begun. The patient was discharged moderately improved 6 weeks after the acute episode. The roentgen results on barium enema examination 9 months after the acute episode are shown in Figure 5*C*.

DISCUSSION

Four cases of intestinal amebiasis are reported which illustrate unusual roentgen features. In 2 of the patients (Cases I and II), showing lesions in the bowel, the cecum was normal roentgenographically (Fig. 2*D* and 3*B*). In the third patient (Case III), the terminal ileum was involved (Fig. 4, *A* and *B*), and in the fourth (Case IV), the clinical and roentgen appearances were those of idiopathic ulcerative colitis (Fig. 5, *A* and *B*).

In acute amebiasis, the only roentgen manifestation may be shallow ulceration, as illustrated by the patient with rectal ulceration only. Amebiasis may resemble idiopathic ulcerative colitis, or may be concurrent with it.[2] The concurrent amebic infestation in the fourth patient was not diagnosed until 18 days after the onset of the acute episode, despite a rectal biopsy and repeated stool examinations. The addition of anti-amebic drugs to the therapy for ulcerative colitis resulted in distinct improvement of symptoms.

In the more chronic phase, amebomas may occur in the colon without obvious cecal involvement (Case I). These amebomas may be plaque-like and could be mistaken for metastatic implants, or they may be annular and be mistaken for primary carcinomas. Although involvement of the terminal ileum in the third patient was unusual, such involvement has been reported previously in amebiasis.[8,12] Thus, if a contracted cecum is demonstrated, involvement of the terminal ileum should not eliminate the differential diagnosis of amebiasis. Tuberculosis, regional colitis, idiopathic ulcerative colitis, right-sided diverticulitis, and periappendiceal infections may also produce a contracted cecum.

SUMMARY

Examples are shown of amebiasis in which unusual roentgen features resemble

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Fig. 4. Case III. Barium enema examination. (*A*) Pre-evacuation roentgenogram. (*B*) Post-evacuation roentgenogram. The cecum is shrunken and deformed (large arrow). Nodular irregularity of terminal ileum with swollen edematous mucosal folds (small arrows).

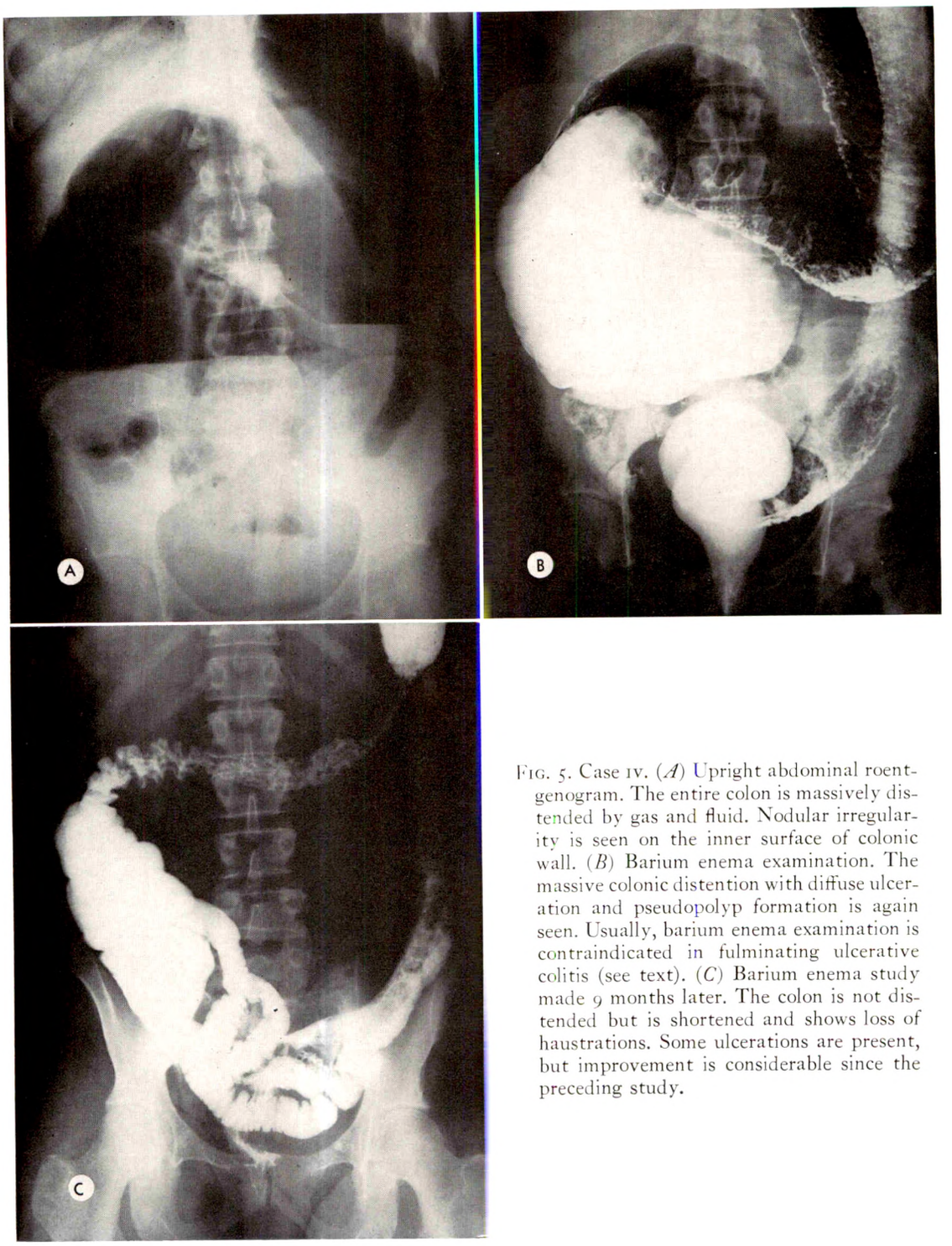


FIG. 5. Case IV. (*A*) Upright abdominal roentgenogram. The entire colon is massively distended by gas and fluid. Nodular irregularity is seen on the inner surface of colonic wall. (*B*) Barium enema examination. The massive colonic distention with diffuse ulceration and pseudopolyp formation is again seen. Usually, barium enema examination is contraindicated in fulminating ulcerative colitis (see text). (*C*) Barium enema study made 9 months later. The colon is not distended but is shortened and shows loss of haustrations. Some ulcerations are present, but improvement is considerable since the preceding study.

those of other diseases of the bowel. Amebiasis should be strongly considered in the differential diagnosis when roentgen examination has demonstrated any of the following: (a) ulceration of the colon, regardless of cecal involvement; (b) contracted cecum, regardless of normal or abnormal terminal ileum; and (c) multiple tumors or multiple constricted areas in the colon, regardless of normal or abnormal cecum.

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LIPOMAS OF THE GASTROINTESTINAL TRACT*

AN ANALYSIS OF SEVENTY-TWO TUMORS

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LIPOMAS are among the benign tumors of the gastrointestinal tract which may cause symptoms. An awareness of this phenomenon coupled with appreciation of the roentgenographic features may allow a relatively high level of security in the clinical diagnosis of this condition. Having been involved in the clinical problem and roentgenographic and pathologic observations in several cases, we were stimulated to make a comprehensive study on the subject of lipomas of the gastrointestinal tract as derived from an aggregate of 72 lipomas in 70 patients.

The material studied was obtained from two sources as follows: (1) the clinical and surgical experience over periods ranging from 10 to 17 years in 6 hospitals* of the Twin Cities of Minnesota (yielding the "clinical series") and (2) the necropsy experience of 4 hospitals† from the same area (yielding the "necropsy series").

OBSERVATIONS

PATHOLOGIC ASPECTS

The tumors are similar to lipomas in other portions of the body including the subcutaneous tissue. In the gastrointestinal tract, the characteristic primary locations are usually submucosal and infrequently subserosal.

The lesion is usually a solitary discrete mass of soft consistence. The cut surface is yellow, lobulated and has the appearance of adipose tissue. Submucosal lesions (Fig. 1, *a* and *b*; and 2, *a* and *b*) protrude toward the lumen and are covered by the mucous membrane. Secondary mucosal ulceration and/or hemorrhage may occur, but this feature is uncommon. Those tumors which occupy a subserosal portion may lie at the junction of the bowel with the mesentery, making it impossible at times to determine whether the tumor arose in the wall of the bowel or in the attached mesentery.

In our series, the size of the lipomas varied considerably, the smallest being 0.5 cm. in diameter and the largest measuring 5 × 8.5 × 14 cm. Of the 68 lipomas in which size was recorded, 9 were less than 1 cm. in diameter, 17 were between 1.0 and 1.9 cm., and 42 of the tumors were 2.0 cm. in diameter, or larger. Eight of the tumors measured more than 5.0 cm. in diameter.

Histologically, lipomas of the gastrointestinal tract exhibit the structure of well differentiated adipose tissue.

The 72 gastrointestinal lipomas in our study were found in 70 patients. In each of 2 cases, 2 lipomas were found. In 1 of these cases, a lipoma was present in the colon and a second in the duodenum. In the second case, 2 separate lipomas were present in the colon. Four other patients had more than 1 lipoma but because in each of these cases the tumors were clustered closely together, they were considered, for purposes of this study, as a single lesion. In 1 case, such accumulations were in the duodenum, in 2 cases in the ileum, and in the fourth case, in the colon.

In our material the 72 lipomas were distributed as follows: 2 (2.8 per cent) were found in the esophagus, 6 (8.3 per cent) in

* The names of the hospitals were Ancker, University of Minnesota, Hennepin County General, Minneapolis Veterans, Charles T. Miller and St. Joseph's.

† The first 4 hospitals named in the above footnote.

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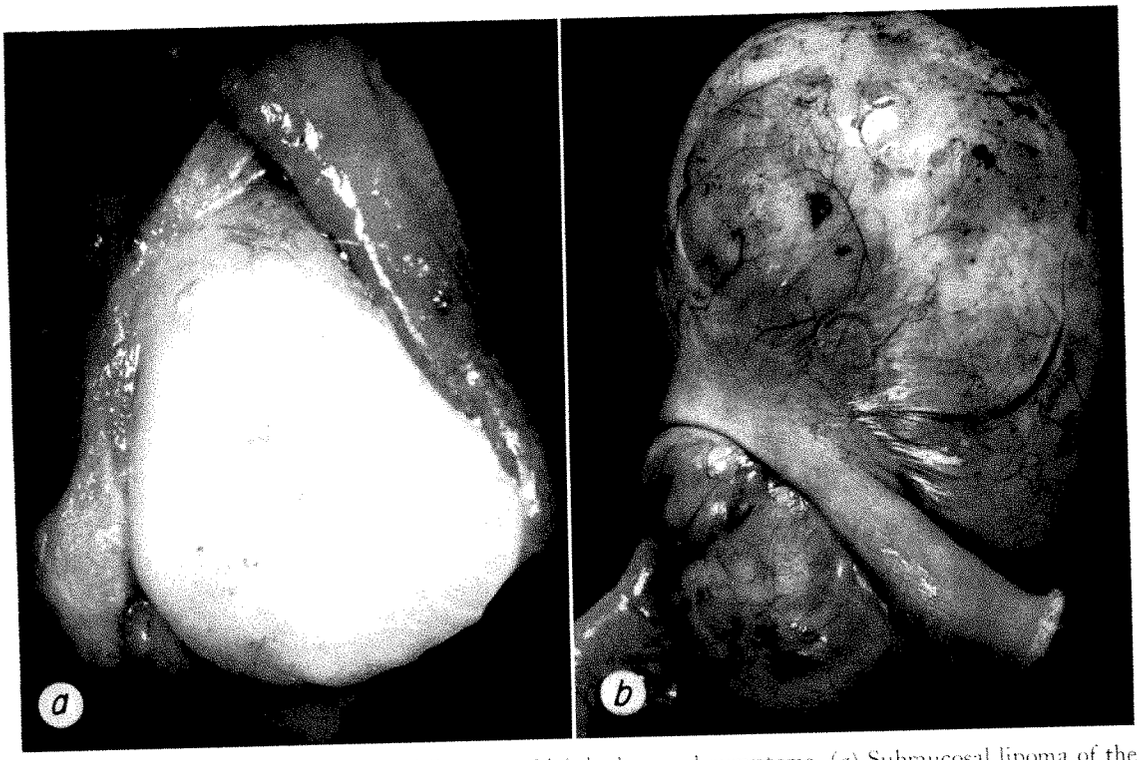


FIG. 1. Representative gastrointestinal lipomas which had caused symptoms. (*a*) Submucosal lipoma of the stomach from a 58 year old man. The tumor has been sectioned to show its relationship to the overlying mucous membrane. (*b*) Segment of ileum and large subserous lipoma in a 24 year old man. Tumor characteristically is well encapsulated. It has caused compression of the involved segment of the ileum.

the stomach, 18 (25 per cent) in the small bowel, and 46 (63.9 per cent) in the colon. It is apparent from our study and those of Weinberg and Feldman[9] and of Mayo and associates[5] that these tumors are more common in the lower than in the upper part of the tract, as lipomas of the colon were about two and one-half times more common than lipomas of the small bowel (Fig. 3).

Of the 6 lipomas of the stomach in our study, 5 involved the body of the stomach and 1 the pyloric antrum. Among those involving the body, 3 were located on the greater curvature, 1 on the lesser curvature, and 1 on the anterior wall. Of the 18 tumors of the small bowel, 8 were found in the duodenum and 10 in the ileum.

INCIDENCE AND SEX DISTRIBUTION

In the clinical series, the 37 lipomas were found in 36 patients, representing an incidence of 1 case in about 25,000 hospital admissions.

In the necropsy series, the 35 lipomas were found in 34 patients, an incidence of 1 case in about 600 necropsies. The incidence in our necropsy series corresponds closely to that reported by Weinberg and Feldman,[9] who reviewed 232 lipomas of the gastrointestinal tract in reported necropsy material.

If one excludes the 17 cases derived from the Minneapolis Veterans Hospital, each of which occurred in the male sex, the remaining cases are almost equally divided between the two sexes. Weinberg and Feldman's[9] and Mayo and associates'[5] series each showed a very slight preponderance among female subjects.

AGE DISTRIBUTION

In our clinical series, the ages of the patients ranged from 16 to 83 years, the median age being 65 years, and of these, only 5 were under 50 years of age. Mayo's study of 164 clinical cases of gastrointes-

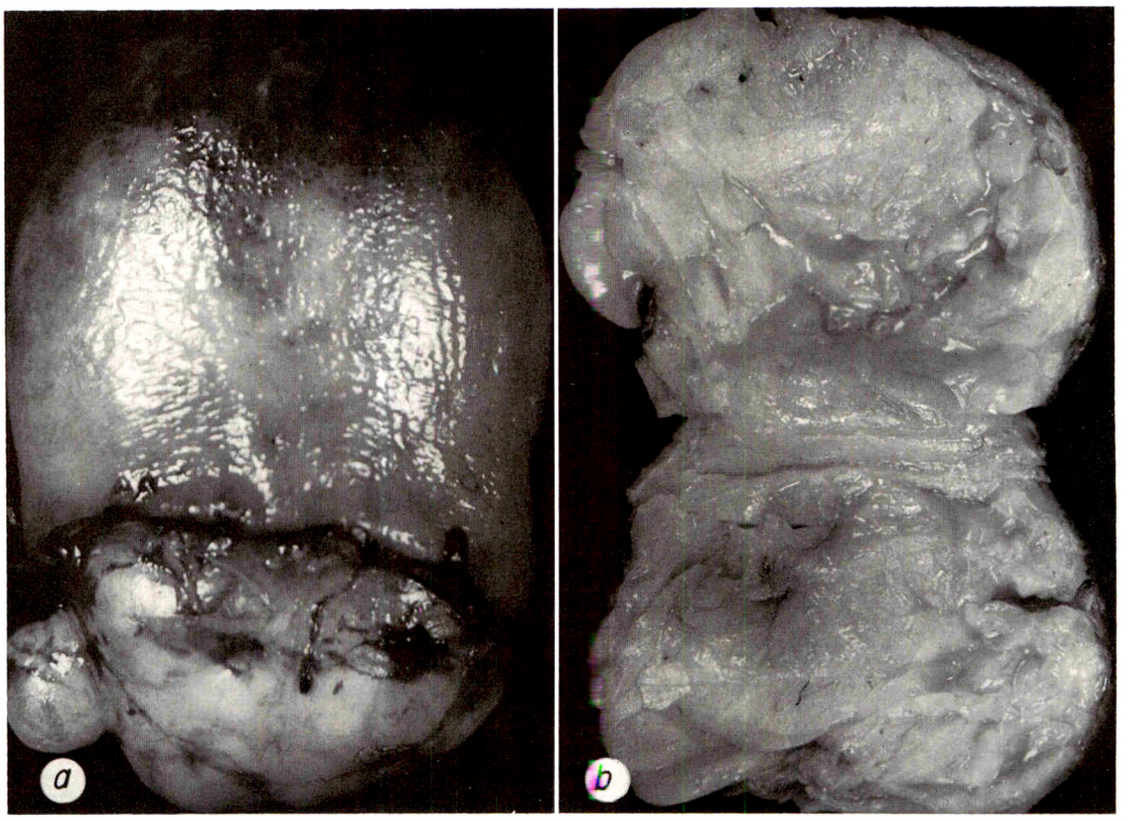


Fig. 2. Lipoma of the ascending colon in a 61 year old woman. Roentgenogram shown in Figure 7. (*a*) Tumor is submucosal and after excision protrudes as a discrete lobulated mass beneath the line of resection. In the upper portion of the illustration, the mucous membrane capping the tumor is present. It shows multiple areas of superficial erosion and secondary hemorrhage. (*b*) Cross section through the tumor shows it to be lobulated in structure. In the fresh state the tumor was yellow, fatty and readily pliable.

tinal lipomas showed a peak incidence in the seventh decade with a range in age from 18 to 85 years.[5]

SYMPTOMS

In 25 of the 36 patients of our clinical series, gastrointestinal lipomas had caused symptoms, abnormal signs, or both. In concert with the findings of Mayo and associates,[5] the incidence of symptoms was directly proportional to the size of the tumor. Of the 9 lipomas under 1.0 cm. in diameter in our clinical series, none had caused symptoms. Over half of those between 3.0 and 4.0 cm. in diameter and three-fourths of the tumors larger than 4.0 cm. in diameter had caused symptoms. The anatomic location of the tumor did not have an obvious influence either in predisposing to or precluding the occurrence of symptoms. Clinical abnormalities encountered in our clinical series included 13 instances of bleeding, 10 of partial intestinal obstruction, 11 of pain as a prominent feature, and in 1 instance, a mass was palpable (Fig. 4). Each of the esophageal lipomas had caused symptoms. Half of the 6 gastric lipomas had caused no symptoms. Two of the 8 lipomas in the duodenum yielded symptoms, and 5 of the 10 in the ileum were symptomatic. Of the 46 lipomas of the colon, 13 (28 per cent) had caused symptoms. There was no distinct relationship between the portion of colon involved and the production of symptoms, except that neither of the 2 rectal lipomas had caused symptoms. There was also no specific relationship between the location of

the tumor and the type of symptoms encountered.

The literature emphasizes that intussusception is a common complication of intestinal lipomas (up to one-third of the cases),[2,7] but uncommon when the tumor is primary in the stomach.[6] In our series of 72 lipomas there were only 4 instances of intussusception, each associated with pain or partial intestinal obstruction. In 3 of these, the lipoma arose in the ileum. This segment of bowel became intussuscepted into the colon and was associated with gangrene of the bowel and perforation. In the fourth case of intussusception, the lipoma arose in the mid-ascending colon.

The clinical features of our cases of gastrointestinal lipomas were not specific. The majority of patients were not seriously ill, and pain, when present, was not particularly severe, except in cases of intussusception. Bleeding was common, but severe anemia was seldom encountered. In no instance had complete obstruction of the bowel resulted, even among those cases with intussusception.

It is reported that severe, acute gastrointestinal bleeding, requiring emergency measures, has been associated with gastric lipomas.[1,6,10] When the tumor arises in sites other than the stomach, loss of blood may be appreciable but seldom occurs abruptly. In the stomach, obstructive symptoms may

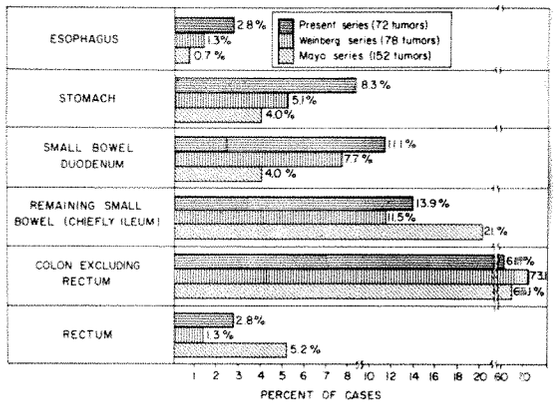


Fig. 3. Anatomic distribution of 72 gastrointestinal lipomas of present study compared with those in series of Weinberg and Feldman[9] and of Mayo and associates.[5]

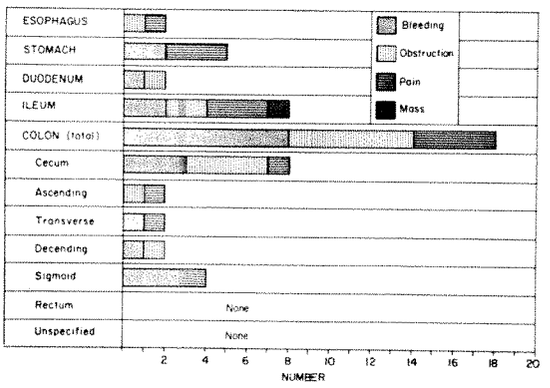


Fig. 4. Thirty-five symptoms occurring in 25 patients with symptomatic gastrointestinal lipomas according to the site of the tumor. Colonic tumors shown both as total and according to anatomic subdivisions.

result from the presence of the tumor mass in the antrum, but intussusception is rare.[6] Nonspecific abdominal distress is reported as a frequent symptom among patients with lipomas of the gastrointestinal tract, regardless of the primary site. Change in bowel habits with constipation, or less frequently, diarrhea was not uncommon.

It is obvious from the foregoing that the only methods by which a diagnosis of gastrointestinal lipoma could be made prior to surgical removal would be either by direct examination endoscopically (with biopsy) or roentgenographically. Endoscopic examination is applicable in tumors of the esophagus, stomach, or rectosigmoid.

Roentgenologic Findings

Roentgenographic examination was done in each of the 36 patients in the clinical series. In 12 of these, the lesion was called a polyp, and it was impossible to state whether the lesion was benign or malignant. In 6 additional cases, the tumor was considered to be "probably benign." In 5 others, a vague lesion was described, but no specific diagnosis was made. In each of 4 instances, the lipoma was not visualized, although another lesion (the one causing symptoms) was identified. The lipoma was then found at operation. In 3 cases, a roentgenographic diagnosis of cancer was incorrectly made. The true nature of the

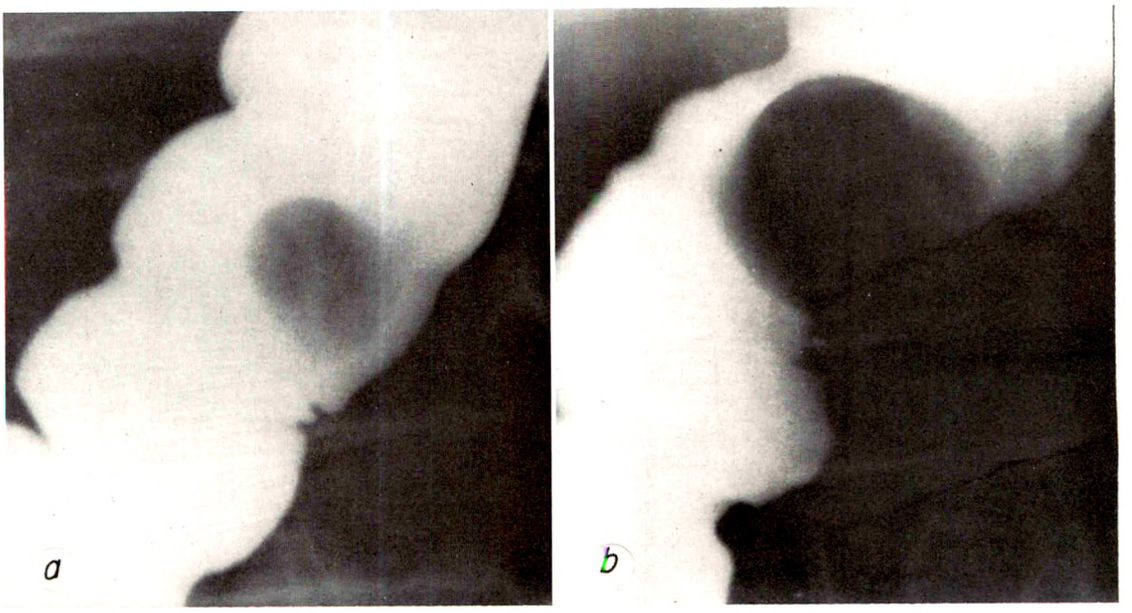


Fig. 5. Lipoma of splenic flexure of colon. (*a*) Roentgenoscopic spot film without compression reveals a 2 cm. sessile submucous lipoma. (*b*) There is flattening and altered configuration of the tumor secondary to external compression, a characteristic roentgenologic feature of gastrointestinal lipomas.

lesions was suspected or a definite diagnosis of lipoma was made in 6 of the 36 cases studied roentgenographically. In several cases not correctly diagnosed as lipoma, the lesion had been described as soft and compressible. In retrospect and with experience gained, we are of the opinion that in some of these cases, the roentgenologic features were characteristic of lipoma.

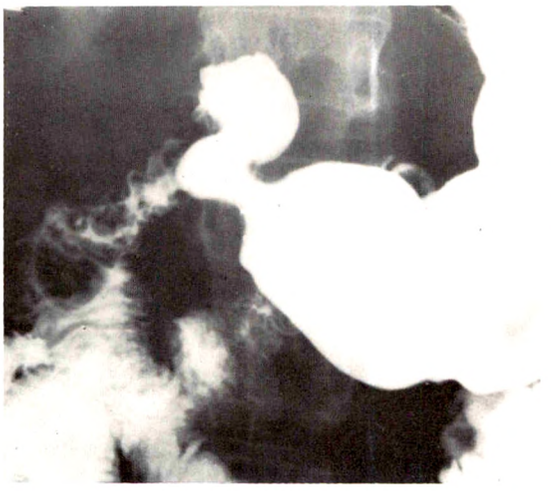


Fig. 6. Pedunculated 3 cm. lipoma in the descending limb of the duodenum which intermittently underwent intussusception into the third portion of the duodenum. Multiple associated leiomyosarcomas of the stomach and small bowel were present in this patient.

Only the submucosal type of gastrointestinal lipoma lends itself to roentgenologic diagnosis (Fig. 5, *a* and *b*; 6; and 7). While the occasional lipoma is of sufficient mass and radiolucence to allow the radiologist to suspect the correct diagnosis on a routine abdominal roentgenogram, barium contrast studies remain the best means of establishing the diagnosis. Margulis and Jovanovich[4] have utilized the inherent radiolucency of these tumors to advantage in establishing a roentgenographic diagnosis. They employ water enema and a low kilovoltage technique, but it is doubtful whether this method will ever replace the conventional barium enema examination.

While the definitive diagnosis of lipoma cannot always be made roentgenographically, certain features are often present which should alert the radiologist to the likelihood of this tumor. A knowledge of these features has enabled the correct diagnosis to be made preoperatively in the last 6 cases of gastrointestinal lipoma we have encountered.

Because of the pliable consistency of the

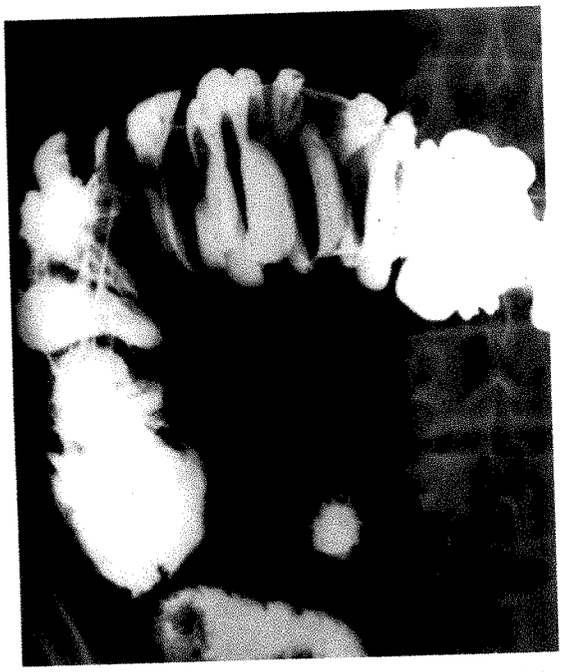


Fig. 7. Pedunculated huge submucous lipoma of the ascending colon with intussusception into the transverse colon. This tumor, which was present in a 61 year old woman, had caused intermittent attacks of colicky abdominal pain. Illustrations of pathologic specimen in Figure 2.

submucosal lipoma, its contours and configuration are frequently altered by peristalsis, an important roentgenologic manifestation, aptly termed the "squeeze sign." This characteristic is pathognomonic of submucous lipomas and does not occur with other mucosal tumors such as polyps or solid submucosal tumors, for example, leiomyomas. In addition, the mucosa overlying a submucous lipoma is frequently stretched so smoothly that barium is unable to adhere to its surface, thereby making it impossible to identify the tumor in all roentgenograms of the examination. If ulceration of the mucosal surface over the lipoma occurs, this process may be demonstrable roentgenologically.

Repeated intussusception or ulceration may cause an inflammatory reaction in the tumor and alter its characteristically soft consistence. In this circumstance, the tumor may be indistinguishable roentgenographically from solid polypoid tumors.

SUMMARY

Gastrointestinal lipomas constitute an uncommon and benign lesion which may cause symptoms like those resulting from malignant tumors.

In a study of 72 tumors in 70 patients, the tumor was found predominantly in the small and large intestines. Symptoms such as bleeding, pain, and obstruction occur in direct proportion to the size of the tumor.

The most reliable means of identifying gastrointestinal lipomas is by roentgenographic study in which the relative radiolucency of the fatty tissue as well as the compressibility of the tumor are helpful signs for the suspicion of this tumor.

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RETROPERITONEAL FIBROSIS FOLLOWING SCLEROSING INJECTIONS FOR INGUINAL HERNIA AND HEMORRHOIDS*

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INSTANCES of idiopathic retroperitoneal fibrosis continue to occur, although in sporadic numbers.[1,4,9] An unusually large group, 30 cases proved at surgery or necropsy, has been reported from the Mayo Clinic.[8] Many types of diseases can mimic retroperitoneal fibrosis, but long-term check-up and biopsies will usually establish the correct diagnosis.[10,15] Cases of unusual types of benign, retroperitoneal fibrosis, some with actual blockage of aortic and iliac arteries, are described in recent papers.[2,12,13,14,17,21]

For the first time, an etiologic factor has been identified which accounts for some instances of retroperitoneal fibrosis. Sansert (methysergide maleate), an effective agent for vasodilatory headaches or migraine, has been found to block ureters and present an identical picture to previous descriptions of retroperitoneal fibrosis.[7,22,24] A remarkable finding was that the severe hydronephrosis would recede to a normal state without surgery after discontinuing the Sansert.[22] It is clear, therefore, that in future instances of retroperitoneal fibrosis careful investigation of other possible drug etiologies will be required. Recent cases associated with necrotizing vasculitis[19] and systemic collagen disease[18] reinforce the hypothesis that other cases may be caused by a variety of drugs and that more careful histories should be elicited.

Recently, a second new factor in the formation of fibrosis previously classified as idiopathic has been recognized by the author. Two cases of retroperitoneal fibrosis were encountered which had been previously injected with sclerosing solutions, one for a hernia and the other for hemorrhoids.

REPORT OF CASES

CASE 1. R. G., a 56 year old man, was admitted to Baptist Hospital (#36180) in November, 1964 because of difficulty in micturition for several months. He complained of frequency of urination every 30 minutes with a small urinary stream at intermittent intervals. On physical examination the prostate was not enlarged and was rubbery in consistency. A fullness could be palpated in the suprapubic area extending almost to the umbilicus, as if a distended bladder were present. However, a previous intravenous urogram in the office did not show a distended bladder, but rather a bladder which was compressed by surrounding pressure (Fig. 1, *A*, *B* and *C*). No hydronephrosis was found, although the ureters were slightly dilated due to extrinsic pressure just above the base of the bladder (Fig. 1, *A*, *B* and *C*). A cystogram and cystoscopy confirmed the extrinsic pressure which caused a pear-shaped appearance of the bladder. The bladder capacity was only 150 cc. without significant residual urine after voiding. A retrograde urethrogram (Fig. 1*D*) demonstrated elevation of the bladder neck above the pubic symphysis, due mainly to elongation of the bulbous and membranous portions of the urethra. The distance between the verumontanum and the bladder neck was not increased. The picture was not that of elongation of the prostate but rather elevation of the prostate from the external sphincters of the pelvic diaphragm. No bladder neck or urethral obstruction was present, although a 2 cm. stone was found in the fundus of the bladder. A barium enema study showed extrinsic pressure and high fixation of the sigmoid (Fig. 1*E*).

The patient stated in his history that 12 years before a naturopathic physician had injected a sclerosing solution around a right inguinal hernia twice a week for about 7 weeks. He remembered becoming severely ill with abdominal distention which subsided spon-

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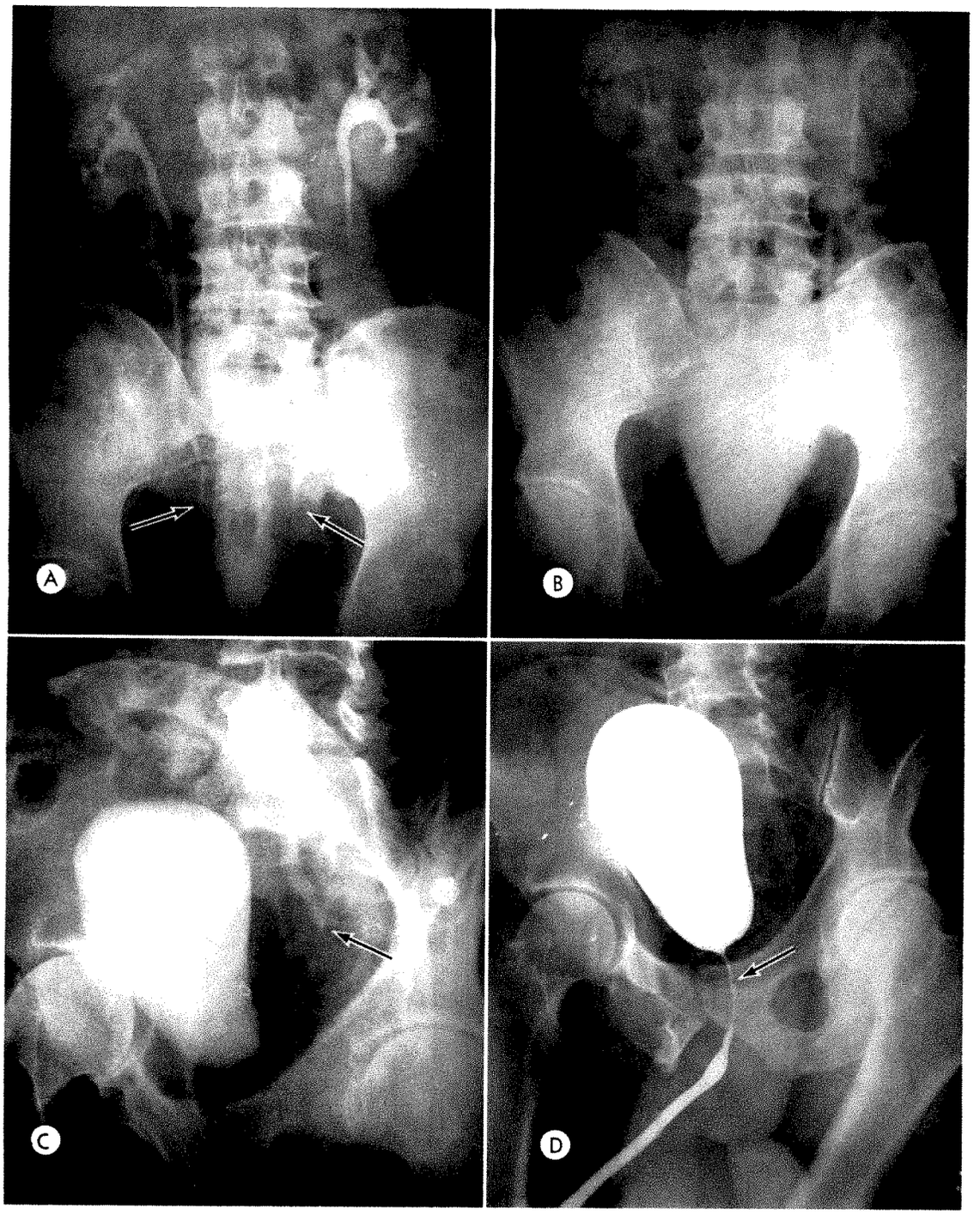


FIG. 1. Case 1. (*A*) A 20 minute intravenous urogram shows slightly dilated ureters, partially blocked just above the bladder (arrows). The lower ureters are pushed medially. (*B*) The pear-shaped bladder is well visualized on a 90 minute study. The ureters are still slightly dilated. The base of the bladder is fixed above the pubic symphysis. (*C*) An oblique study shows the hold-up in the left ureter (arrow). The bladder is pushed forward. (*D*) An oblique urethrogram shows that the distance between the bladder neck and verumontanum (arrow) is not increased. However, the distance between the veru and the bulbous urethra is elongated causing, in effect, a long membranous urethra.

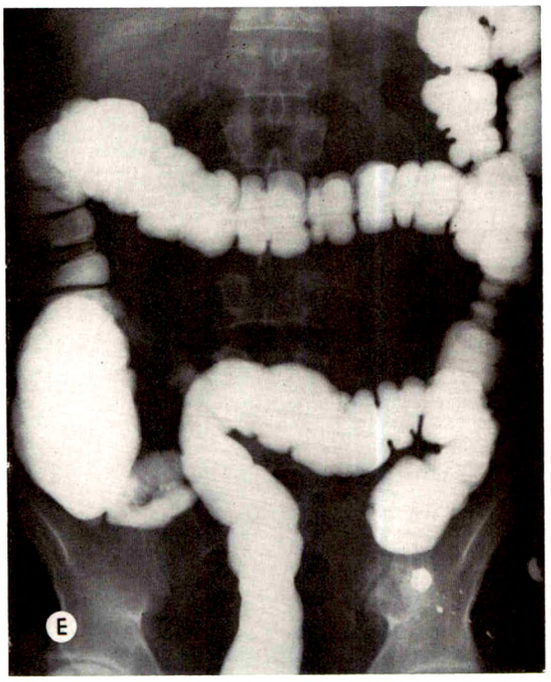


FIG. 1. (*E*) A barium enema examination shows straightening and high fixation of the sigmoid colon. Fluoroscopy confirmed extrinsic pressure against the sigmoid colon.

taneously. The hernia itself was cured. On examination the inguinal cord and testicles were normal. Communications with the naturopath indicated that the sclerosing solution consisted of quinine, urea and silicones.

Because of this history, a diagnosis of retroperitoneal fibrosis, compressing the bladder, ureters and colon, due to the sclerosing solution was made, although a neoplasm could not be ruled out. The bladder was explored through a transverse lower rectus incision. A marked reaction process consisting of fibro-fatty tissue encased and compressed the bladder. Large amounts of fibro-fatty tissue were removed, allowing the bladder to expand. The base of the bladder was dissected free but the ureters were not stripped. The 2 cm. stone was removed from the bladder. On opening the peritoneum above the bladder, no intraperitoneal reaction was found. However, the right gutter was found bound to the internal ring and surrounding muscles where the hernia had been injected.

Histologic sections revealed only fat which was well vascularized and irregular collections of dense fibrous tissue. No foreign body reaction was demonstrated.

The patient did well except for a serious episode of a pneumonitis, possibly due to pulmonary embolism, which required rehospitalization. Under medical management he recovered completely. At a 6 month follow-up, he voided with an excellent stream and the bladder capacity had increased to 300 cc. An excretory urogram showed a fuller bladder which was still pear-shaped; the ureters remained slightly dilated.

Comment. The pear-shaped bladder from extrinsic compression is frequently seen following pelvic fractures with or without a bladder or urethral rupture. The mechanism is accumulation of blood or urine surrounding the bladder area. This patient had no history of any pelvic fractures or urinary tract rupture.

In several other cases, retroperitoneal fibrosis has caused masses in the pelvic region.[10] Hewett and Headstream[11] report a patient with a typical pear-shaped bladder from retroperitoneal fibrosis who eventually required an ileo-conduit. A similar case has been recorded from England.[23] In these cases, no history of injections of a sclerosing agent was obtained, but such a history was probably not solicited.

Pathologic examination revealed no characteristic findings of the sclerosing solution as would be expected from quinine, urea and silicones. Silicones have been known to produce a nonspecific fibrous reaction when injected under the skin in plastic procedures. Although the solution was injected only in the right inguinal region, it is easy to justify an extensive spread in the pelvic region and a surrounding of the bladder. Figure 2, a 25 minute excretory urogram, was made 3 days after a successful cystoscopic extraction of a left ureteral stone; however, it is apparent that a tear had taken place in the left ureter. Extravasation of urine from the left ureter can be seen. More interestingly, the extravasation has spread to the right side of the bladder and caused a right hydronephrosis which had not existed before the stone extraction. At operation, the urine was drained from where it had surrounded the bladder and

the patient had an uneventful recovery. This case illustrates the ease of spread of fluid substances in the pelvic region.

Case II. H. W., a 35 year old obese man, was admitted to Baptist Hospital (admission #39577) March 17, 1965 for evaluation of a persistent, moderate elevation of blood pressure. He had no urinary tract or gastrointestinal symptoms, and physical examination revealed no unusual findings. Urinalysis was normal and a blood urea nitrogen was 17.5 mg. per cent. An intravenous urogram demonstrated early dilatation of both ureters from obstruction at the ureterovesical junction and a compressed bladder in the shape of a gourd or banana (Fig. 3*A*). A retrograde ureterogram confirmed the low, ureteral obstruction (Fig. 3*B*). A urethrogram showed some elevation of the bladder above the pubic symphysis, although there was no actual elongation of the posterior urethra itself, only of the membranous and bulbous urethra. A barium enema study revealed compression from extrinsic pressure and an elongation with high fixation of the sigmoid colon (Fig. 3*C*).

In view of the similarities with the previous case, the patient was then questioned about injections. He had received approximately 6 rectal injections for hemorrhoids 8 years before, which did effectively shrink the hemorrhoids. The proctologist performing the injections had used 6 per cent phenol in almond oil. Because of such a history, the diagnosis was benign fibro-fatty tissue compressing the bladder, lower ureters and colon. After deliberately losing weight, the patient was explored August 23, 1965 by Dr. L. Stapp with the finding of thickened fatty tissue surrounding the bladder, ureters and colon. No definite freeing of these structures could be done; however, a biopsy from perivesical tissues was obtained. The pathologic report was tissue composed of mature fat cells with some increase in vascularity. The patient's postoperative course was uneventful.

Comment. This case is similar to Case 1 except for a gourd-shaped bladder rather than a pear-shaped structure and injection of hemorrhoids rather than of a hernia. Anatomically, the solution could spread just as in Case 1 if it were injected too deeply. Early blockage of the ureters and a high fixation of the sigmoid colon resulted in both instances.

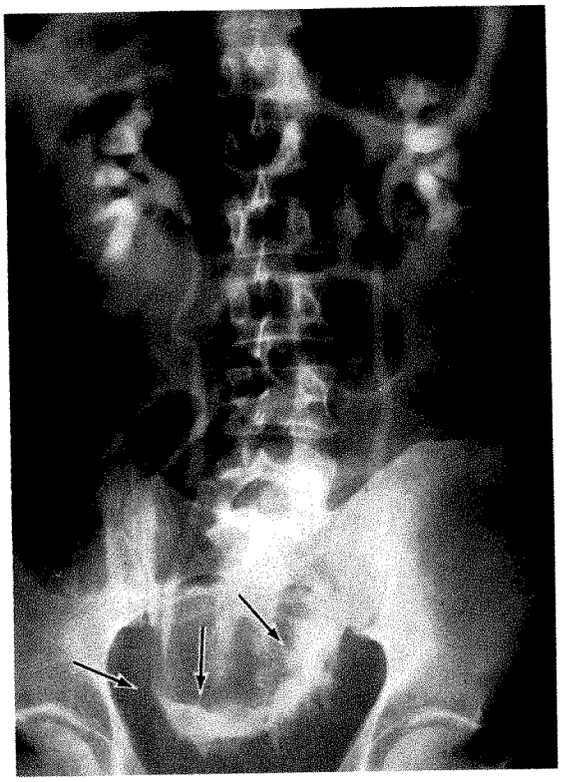


Fig. 2. An intravenous urogram demonstrates extravasation of urine from the left ureter where a stone had been cystoscopically extracted 3 days before. The extravasation extends around the bladder (arrows) and now blocks the right ureter. On previous roentgenograms the right kidney and ureter had been normal.

Discussion

In reviewing the literature, 4 reports encompassing 11 cases were found that were similar to the cases in this report.[5,6,16,20] Some were labeled high fixation of bladder and sigmoid colon with a banana or gourd-shaped bladder.[5,16] One was called Dercum's disease[20] and 5 were labeled a nonspecific rectosigmoiditis.[6] No histories of injections of sclerosing agents were mentioned, but probably such a history was not solicited. Two other cases[11,23] labeled pericystitis probably fit into the same category, although no descriptions of the barium enema studies were provided. In another interesting paper, 2 patients de-

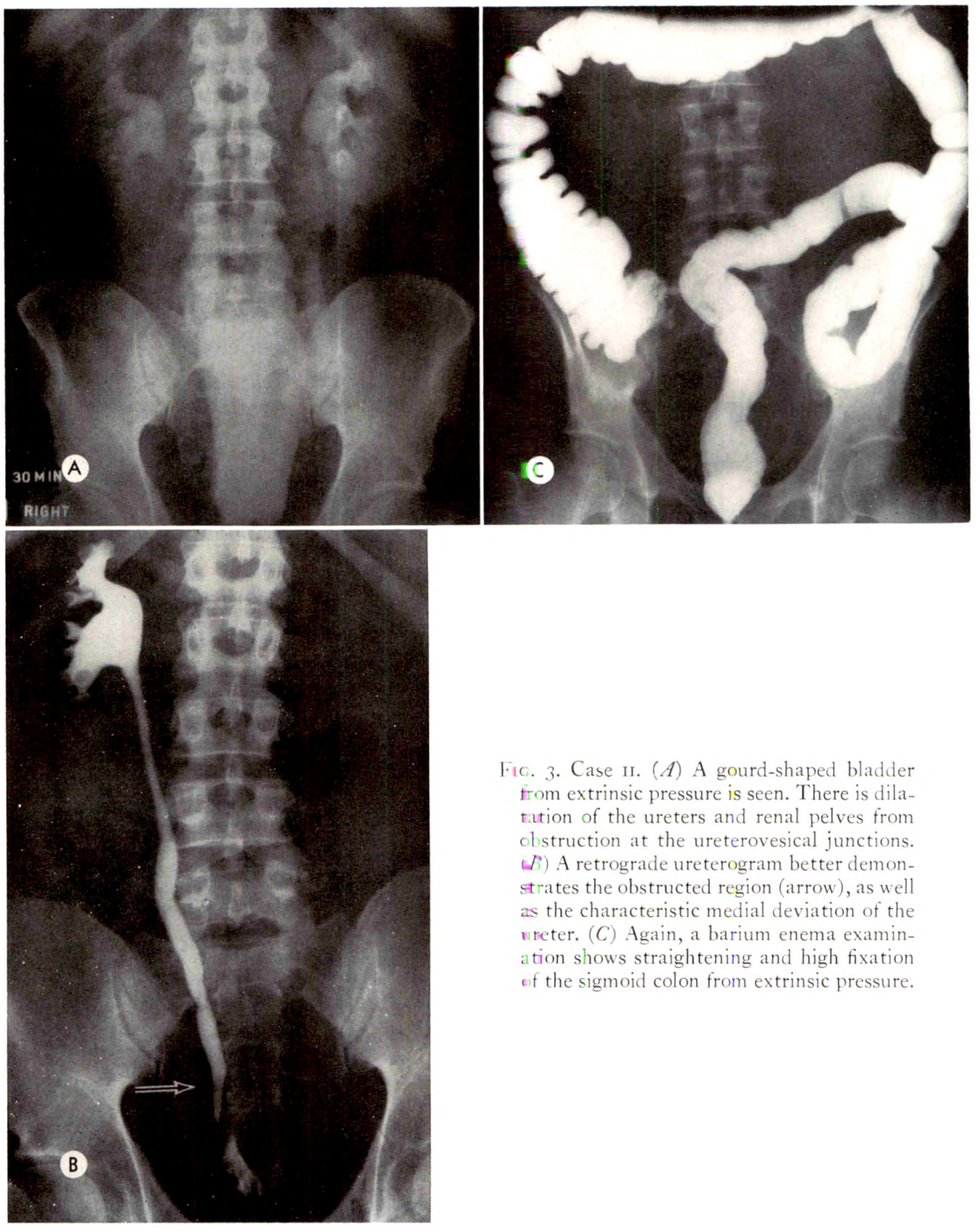


Fig. 3. Case II. (*A*) A gourd-shaped bladder from extrinsic pressure is seen. There is dilatation of the ureters and renal pelves from obstruction at the ureterovesical junctions. (*B*) A retrograde ureterogram better demonstrates the obstructed region (arrow), as well as the characteristic medial deviation of the ureter. (*C*) Again, a barium enema examination shows straightening and high fixation of the sigmoid colon from extrinsic pressure.

veloped lower ureteral obstruction without bladder compression following injections of mineral oil for vaginal prolapse.[3]

In these cases, the diffuse pelvic distribution and the lack of progression of the disease made it difficult to ascertain whether a benign rather than a malignant type of process was involved. Often surgery was necessary to establish that a neoplasm was not present. In the future, the character-

istic roentgen findings correlated with a history of injections of sclerosing agents will establish the entity without the necessity of exploring the patient. Of course, in certain instances of progressive hydronephrosis, urinary diversion will be required.

SUMMARY

Two cases of a fibro-fatty reaction following the injection of a sclerosing agent are reported. Cases labeled high fixation of the bladder and colon or pericystitis from retroperitoneal fibrosis may well be the same entity where no attempt was made to solicit a history of sclerosing injections.

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Dr. Lee Stapp, Miami, Florida, provided the history of Case II.

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A HAZARD OF SILICONE FOAM DIAGNOSTIC ENEMA*

REPORT OF A CASE OF PERFORATION OF THE COLON

By JOHN R. AMBERG, M.D.
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IN 1961 Cook and Margulis[2,3] first reported the use of a silicone foam diagnostic enema for the examination of the rectosigmoid area. This new method is of value for 3 reasons. First, it provides a three-dimensional moulage of the colon. Secondly, the moulage depicts areas beyond the limits of the sigmoidoscope and these are areas in which redundancy of the colon often compromises the roentgenologic examination. Thirdly, it provides a source of cells for cytologic study.[4]

As with any new technique, unforeseen complications are experienced. In the following case report a sigmoid colon perforated by a silicone foam enema is described. Suggestions for the prevention of this complication are recommended.

REPORT OF A CASE

A 53 year old woman had received radiation therapy for a Stage IIB carcinoma of the cervix 1½ years before admission.

The first symptoms related to the bowel occurred 1 year after completion of radiation therapy. These were rectal bleeding, diarrhea, and abdominal pain of increasing severity.

The results of pelvic examination did not suggest recurrent neoplasm. On proctoscopy, a narrow lumen was seen at 13 cm. A roentgenogram of the colon showed constriction in the mid-sigmoid area (Fig. 1). Radiation stricture or primary adenocarcinoma of the sigmoid colon was the diagnosis considered.

A silicone foam enema was given. An 11 cm. segment of the mold was expelled immediately, which, because of its smooth conical tapering, strongly supported the diagnosis of radiation stricture (Fig. 2).

A second portion of the mold was passed 4 days later. A roentgenogram at that time showed a considerable segment of the mold remaining above the stricture (Fig. 3).

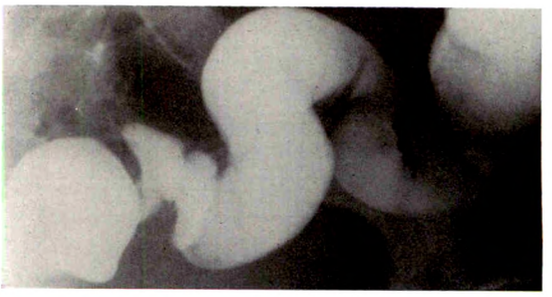


FIG. 1. Constriction in sigmoid colon as demonstrated on spot roentgenogram.

Two days later, the patient was discharged from the hospital, but after 4 days she had to be readmitted because of severe abdominal pain of 12 hours' duration. The abdomen was rigid and the patient was in a state of shock. Free gas was present in the peritoneal space. Retained foam was seen within the gas-distended proximal sigmoid colon (Fig. 4). An immediate laparotomy revealed a perforation of the sigmoid colon and gross contamination of the peritoneal space. No neoplasm was seen in any of the pelvic organs or the colon. A colostomy was done but the patient responded poorly and died immediately. A necropsy was not performed.

DISCUSSION

Perforation of the sigmoid colon, on the basis of radiation damage alone, may occur spontaneously.[1] In the patient described above, the time relationship strongly sug-



FIG. 2. Reconstituted sigmoid moulage. The smooth tapering of the stricture can be seen. The darkly stained foam was that retained within the colon for 4 days.

* From the Department of Radiology of the University of California School of Medicine and the Veterans Administration Hospital, San Francisco, California.

gests that the constricted portion of the sigmoid colon was further damaged by attempts to pass the silicone foam.

At least 3 lessons were learned: (a) to demonstrate the lesion, flow of the foam beyond the area of constriction is not necessary; (b) further trauma to an ischemic bowel associated with a radiation stricture is hazardous; and (c) when any portion of the mold is retained, medical surveillance should be continued.

Retrospectively, with the symptoms and findings described in this patient, an immediate diverting colostomy should have been done regardless of whether a silicone foam enema had been given.

SUMMARY

A fatality associated with the use of a silicone foam diagnostic enema in a patient with a radiation stricture is reported. Although limitation of the enema would be expected to minimize this complication, this method of diagnosis in a radiation-injured colon is definitely contraindicated.



FIG. 3. Residual foam (radiopaque) present above stricture on 4th day after instillation.

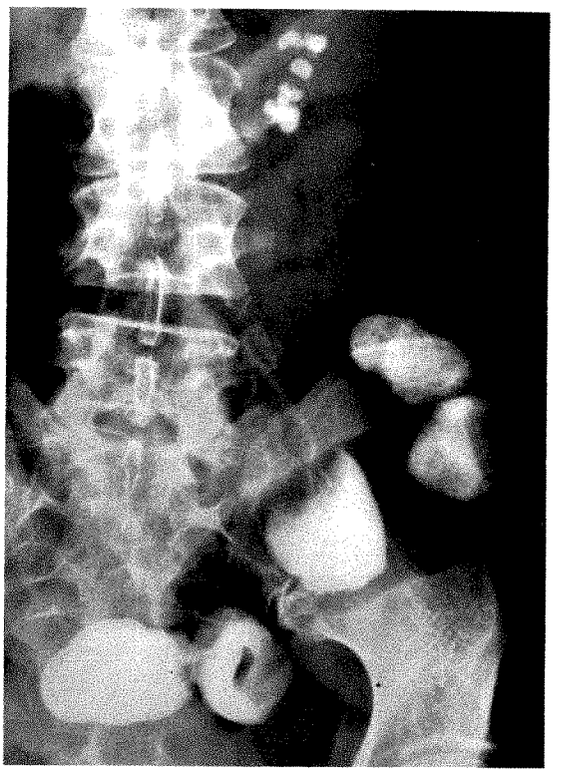


FIG. 4. Residual foam on readmission at time of perforation of sigmoid colon. Contour of mold and distention of descending colon indicate mold is straddling stricture at site of perforation and partially obstructing the colon.

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COMPARISON OF CARBOXY-METHYLCELLULOSE, TANNIC ACID AND NO ADDITIVE IN BARIUM EXAMINATIONS OF THE COLON*

By CARLOS A. PEREZ, M.D., *and* MARVIN J. FRIEDENBERG, M.D.†
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UNTIL recently, concentrations of tannic acid varying from 0.25 to 3.0 per cent were used in barium and air contrast examinations of the colon, because of its astringent properties and improved adherence of the barium to the colonic mucosa.[5,6,13] However, experimental reports[2,4,9] and clinical evidence[11,15] of the toxic effect of high concentrations of tannic acid upon the liver have caused this practice to be discontinued in many institutions.

The addition of methylcellulose and some of its esters to barium mixtures has been recommended in the study of the esophagus,[16] the small intestine,[8] and the colon.[19] The purpose is to improve the suspension of the barium sulfate molecules in water and to obtain homogeneous opacification of the gastrointestinal tract and better coating of the mucosa. This is a report of the results of a double blind comparison of tannic acid, carboxy-methylcellulose, and no additive in 1,000 barium enema examinations.

PROPERTIES OF CARBOXY-METHYLCELLULOSE

Methylcellulose, a methyl ester of cellulose, is a grayish white fibrous powder. This material swells in water and produces a clear to opalescent viscous colloidal suspension. Although this substance is less soluble in hot water, solutions are best prepared by mixing the powder with approximately one-half the amount of required water at boiling temperature, allowing the mixture to soak for about 20 minutes and then adding the remainder of the water cold or as ice. Flakes of methylcellulose separate when the suspension is heated, but the colloid redissolves when cooled.

Methylcellulose and its esters have been widely used in industry and medicine to stabilize and increase the viscosity of suspensions. Methylcellulose is unabsorbable, nonirritating to the intestinal mucosa and has no toxic effect. It has been used as a laxative because of its hydrophilic properties and ability to activate peristalsis by increasing the bulks of the intestinal contents.[16] Sodium carboxy-methylcellulose has properties similar to methylcellulose, differing only in that it is insoluble in gastric juice.[1]

PHARMACOLOGY OF TANNIC ACID

Tannic acid, as used in medicine is really the gallotannic acid, an internal ester of gallic acid. It is present in high concentrations in tea and burgundy.[7]

Tannic acid is a yellowish white powder which has the property of precipitating proteins as well as many heavy metals and alkaloids. It has been employed as an antidote in cases of alkaloid, glycoside and heavy metal poisoning because of the partial precipitation of the poison produced. Due to its protein precipitating properties, tannic acid has been used to produce a protective coating for the intestinal mucosa[7] and to improve the adherence of barium in the colon.[6] Experimental investigations have demonstrated that tannic acid is rapidly absorbed into the blood stream after injection into the stomach or the colon[9,15] and that concentrations higher than 1–2 per cent may result in fatal liver centrilobular necrosis.[11,15]

MATERIAL AND METHODS

Standard USP barium mixtures were

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Table I

CARBOXY-METHYLCELLULOSE, TANNIC ACID AND NO ADDITIVE IN BARIUM ENEMA EXAMINATION OF THE COLON

Age and Sex Distribution of Patients

Age (yr.)	Carboxy-methylcellulose 0.2%	Carboxy-methylcellulose 0.5%	Carboxy-methylcellulose 1%	Tannic Acid 0.25%	No Additive
10–19	5	4	4	5	3
20–29	12	12	18	16	11
30–39	24	26	19	23	24
40–49	42	42	38	45	46
50–59	53	50	41	49	53
60–69	38	38	48	42	36
70–79	20	22	24	17	21
80–more	6	6	8	3	6
Total	200	200	200	200	200
Sex Distribution					
Male	79	73	96	85	74
Female	121	127	104	115	126
	200	200	200	200	200

made with no suspending agent, with the addition of 0.2, 0.5 and 1.0 per cent carboxy-methylcellulose,† and with the addition of a 0.25 per cent solution of tannic acid. The relative viscosity of three samples of each suspension was determined, using a Stormer viscosimeter in a water bath at constant temperatures of 25° C. The stability and settling properties of these suspensions were evaluated by placing 8 cc. of each sample in a test tube and allowing precipitation at room temperature. Roentgenograms of the samples in the tubes were obtained at 1, 3, 5, 10, 20, and 30 minutes, and at 1, 6, and 12 hours. The thickness of the coating material and adhesiveness of the suspensions were investigated by coating a plastic tube with each suspension and allowing settling to occur with the tubes held vertically for 30 seconds. Five photographs were obtained of each of the five samples.

Age and sex distribution of the 1,000 patients included in the clinical portion of this study are shown in Table 1. Preparation of the patients for the barium enema examinations consisted of a liquid and soft food diet for at least 1 day, 1 or 2 ounces of castor oil ingested in the evening prior to the examination, 1 soapsuds enema and 2 enemas with oxphenisatin (3, 3-bis 4-hydroxyphenyl)* the morning of the examination. Two hundred barium enema examinations were done with no additive. Carboxymethylcellulose was used as a suspending agent in 600 barium enema examinations, 0.2, 0.5 and 1.0 per cent of the cellulose ester being used in each of 200 examinations. Two hundred barium enema examinations performed in 1962, when a 0.25 per cent concentration of tannic acid was routinely added, were randomly selected for comparison. The barium suspension consisted of a 20 per cent weight/volume mixture, using USP barium (specific density 1.1).

The same basic routine was used in performing the barium enema examinations: under fluoroscopic control, the barium sus-

† C-M-Cellulose, Type 7 MP. Hercules Powder Co., Hopewell, Va.

* Lavema, Winthrop Laboratories, New York, New York.

TABLE II

CARBOXY-METHYLCELLULOSE, TANNIC ACID AND NO ADDITIVE IN BARIUM ENEMA EXAMINATION OF THE COLON

Criteria in Evaluation of Postevacuation Roentgenograms

	Evacuation of Colon	Mucosal Detail
Excellent	100% Emptying	All Mucosal Folds Well Seen
Good	75–80% Emptying	75% of Mucosal Folds Well Seen
Fair	50% Emptying	50% of Mucosal Folds Well Seen
Poor	Less Than 50% Emptying	Less Than 50% of Mucosal Folds Well Seen

pension was instilled into the colon with gravity pressure until the terminal ileum and/or the appendix filled with contrast material. Spot roentgenograms and table-top roentgenograms were obtained in frontal, lateral and oblique projections. The patient was allowed to evacuate the colon, and a posteroanterior roentgenogram of the abdomen was made. The technical factors were: 25 mas., and about 120 kv., depending on the thickness of the patient.

The postevacuation roentgenograms of these 1,000 examinations were analyzed by one observer with no knowledge of the suspending agent used. The degree of evacuation of the colon and the quality of the mucosal detail were evaluated (Table II).

RESULTS

The viscosities of the different barium mixtures showed no significant difference, whether additive was used or not (Table III).

TABLE III

VISCOSITY OF BARIUM SUSPENSIONS WITH VARIOUS SUSPENDING AGENTS

(Stormer Viscosimeter, 25° C. Temperature)

	Centipoises
Barium with 0.2% carboxy-methylcellulose	1.0188
Barium with 0.5% carboxy-methylcellulose	1.0188
Barium with 1% carboxy-methylcellulose	1.0277
Barium with 0.25% tannic acid	1.0277
Barium without suspending agent	1.0098
Distilled water	.8937

At 1, 5, and 10 minutes the barium suspension with addition of 0.5 and 1.0 per cent carboxy-methylcellulose remained longer in a homogeneous suspension and settling was slower than in samples in which 0.25 per cent tannic acid or no suspending agent was used (Fig. 1). However, after 10 minutes no significant difference was appreciated in any of the samples.

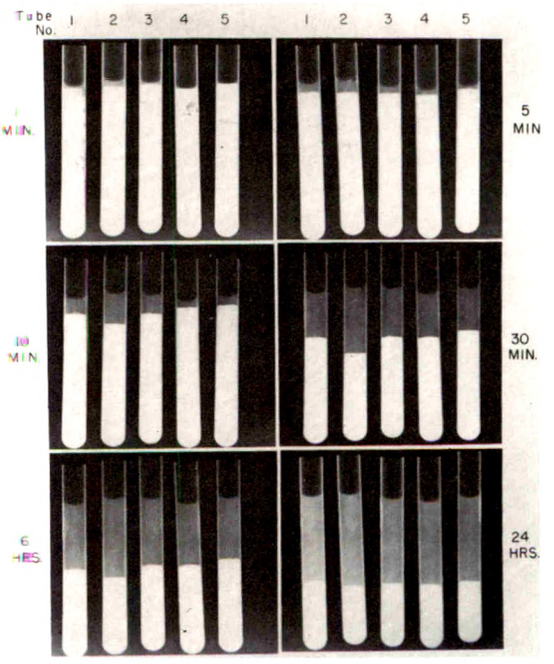


FIG. 1. Tube No. (1) No additive; (2) 0.25 per cent tannic acid; (3) 0.2 per cent carboxy-methylcellulose; (4) 0.5 per cent carboxy-methylcellulose; (5) 1 per cent carboxy-methylcellulose. Settling and stability of different barium suspensions. Notice less early settling of barium with 1 per cent carboxy-methylcellulose (Tube No. 5). There is rapid settling in all samples after 10 minutes.

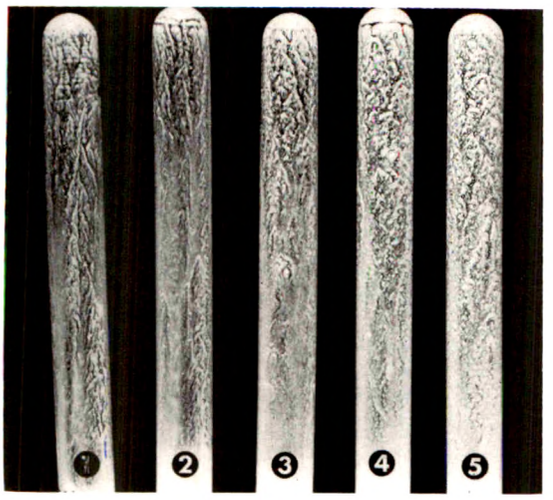


Fig. 2. Photograph of plastic test tubes coated with barium suspensions with (1) No additive; (2) 0.25 per cent tannic acid; (3) 0.2 per cent carboxy-methylcellulose; (4) 0.5 per cent carboxy-methylcellulose; (5) 1 per cent carboxy-methylcellulose. Better adherence of barium with carboxy-methylcellulose is demonstrated.

These suspensions were compared with several fine particle barium commercial preparations (micropaque, barosperse, baroloid), and the latter group was found to be significantly more stable.

The adhesiveness of the different samples containing carboxy-methylcellulose was more uniform than with no additive agent. No significant bubbling or foaming was noted in the samples. The degree and uniformity of the coating of the plastic tubes coated with barium containing 0.5 and 1.0 per cent carboxy-methylcellulose was better than those with no additive or 0.25 per cent tannic acid (Fig. 2).

Figure 4 shows the comparative results of the mucosal coating on postevacuation roentgenograms of the 1,000 barium enema examinations. Satisfactory mucosal detail was present in patients in whom 0.5 and 1.0 per cent carboxy-methylcellulose was used (56.6 per cent and 63.5 per cent excellent and good roentgenograms, respectively). The percentages are comparable to the group in which 0.25 per cent tannic acid was added (65.5 per cent excellent and good roentgenograms) and significantly better than in the patients in whom no additive was used (42.5 per cent excellent and good roentgenograms).

The degree of evacuation of the colon was essentially the same in all of the cases evaluated (84 to 90 per cent excellent and good evacuation) (Table IV).

Discussion

Optimal roentgenographic examination of the colon requires barium suspensions which provide homogeneous opacification of the bowel and excellent coating of the mucosa on postevacuation roentgenograms. Brown[3] demonstrated that reducing the diameter of the barium particles below 1 micron does not improve the coating property. The addition of some colloidal compounds to the barium suspension increases

Table IV

Carboxy-methylcellulose, tannic acid and no additive in barium enema examination of the colon

	Degree of Evacuation of the Colon							
	Excellent		Good		Fair		Poor	
	No. of Examinations	%	No. of Examinations	%	No. of Examinations	%	No. of Examinations	%
Carboxy-methylcellulose 0.2%	120	60.0	48	24.0	26	13.0	6	3.0
Carboxy-methylcellulose 0.5%	133	66.5	45	22.5	17	8.5	5	2.5
Carboxy-methylcellulose 1.0%	141	70.5	28	14.0	23	11.5	8	4.0
Tannic Acid 0.25%	138	69.0	36	18.0	21	10.5	5	2.5
No Additive	128	64.0	48	24.0	14	7.0	10	5.0

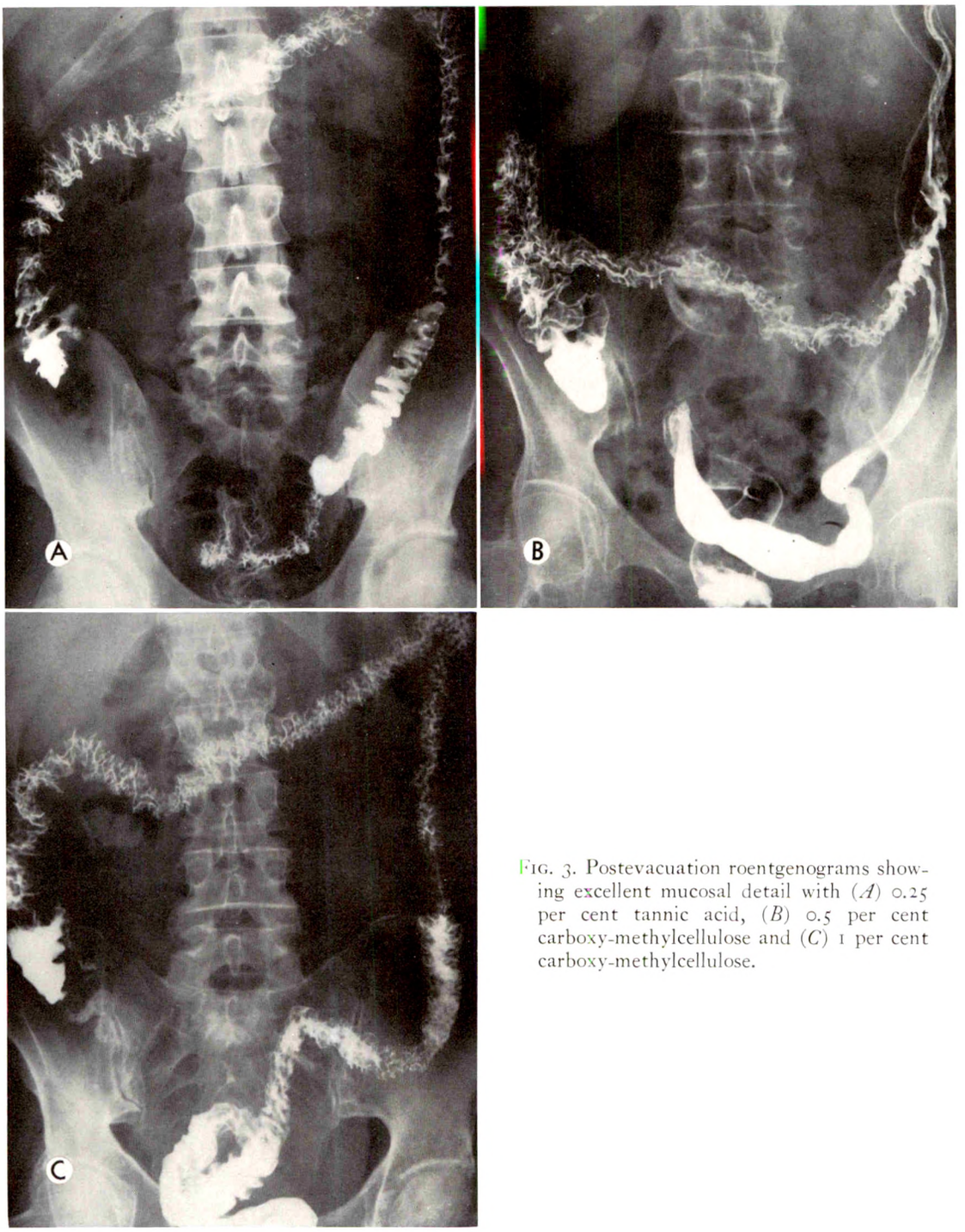


FIG. 3. Postevacuation roentgenograms showing excellent mucosal detail with (*A*) 0.25 per cent tannic acid, (*B*) 0.5 per cent carboxy-methylcellulose and (*C*) 1 per cent carboxy-methylcellulose.

the negative electrokinetic charge on the barium sulfate particles. This causes the particles to repel each other and prevents flocculation of the suspension.[3] Larger particles might offer substantial advantages, if they can be made to remain in suspension.[13] A considerable number of substances, including methylcellulose, pectin, heparin, mucin, tragacanth, mineral oil, tannic acid, aluminum silicate, starch,

sodium carbonate, polyoxyethylene derivatives, gelatin, etc., have been tried in an attempt to improve the miscibility and suspension of the barium.[13]

At least 20 commercial preparations of barium are available, having different particle sizes and a variety of suspending agents. Satisfactory barium enema examinations with these compounds have been reported previously, although the increased cost may be a disadvantage.[18] The use of carboxy-methylcellulose as a suspending agent has been described,[1,10,17] but its practicability has not been emphasized. This colloid is harmless,[1,16] relatively inexpensive and easy to prepare in solutions.

In a double blind evaluation of the postevacuation roentgenograms of 1,000 barium enema studies, carboxy-methylcellulose in concentrations of 0.5 and 1.0 per cent provided barium coating of the colon mucosa similar in quality to 0.25 per cent tannic acid (Table III) (Fig. 3, *A*, *B* and *C*). These results are significantly better than those obtained with the same barium suspension without additive or when only 0.2 per cent of carboxy-methylcellulose was present.

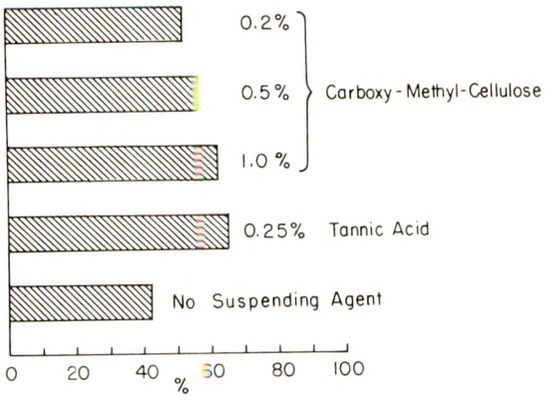


Fig. 4. Graph showing percentage of excellent and good quality of mucosal detail on postevacuation roentgenograms.

Less layering of barium and more homogeneous opacification of the colon was obtained when a suspending additive was employed. The same satisfactory results have been observed in double contrast ex-

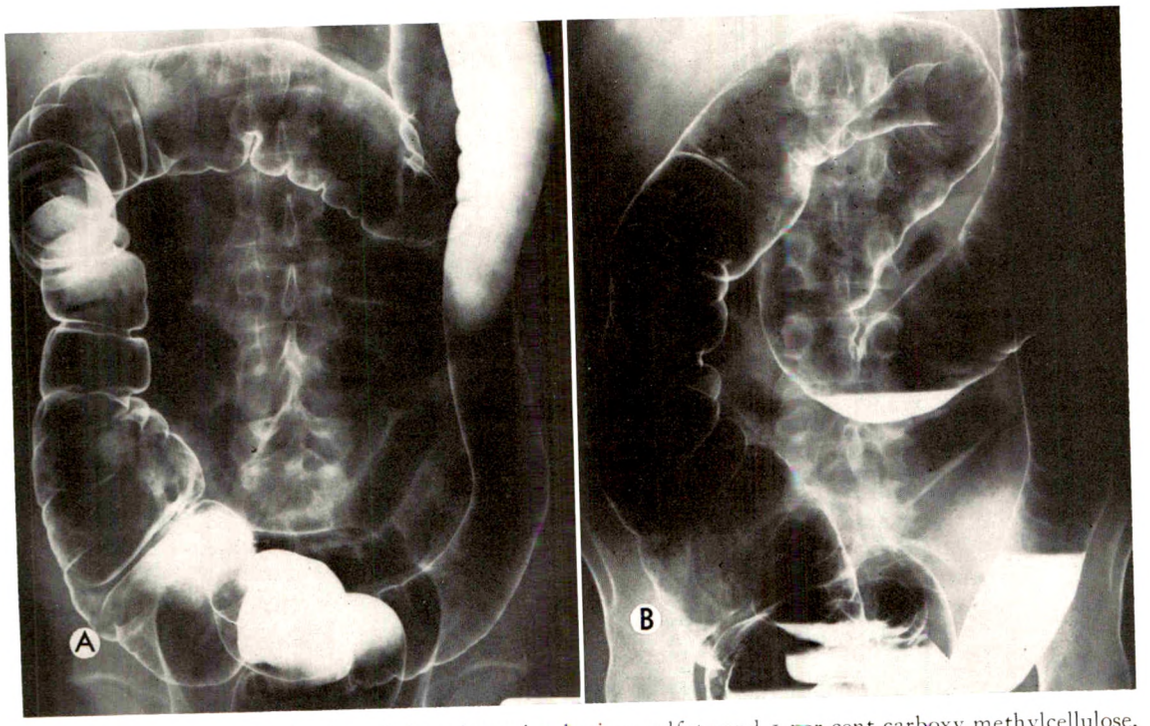


Fig. 5. Air contrast examination of the colon using barium sulfate and 1 per cent carboxy-methylcellulose. (*A*) Frontal erect and (*B*) supine roentgenograms demonstrating excellent coating of colonic mucosa.

aminations of the colon (Fig. 5, *A* and *B*).

Evacuation was equally satisfactory in all groups of patients evaluated (Table IV), probably due to better contraction of the bowel induced by maximum distention. Although a good evacuation is necessary for adequate mucosal visualization, mucosal detail requires, in addition, adherence of the barium particles to the mucosa. Therefore, satisfactory evacuation does not imply good mucosal detail. The postevacuation roentgenogram must be obtained as soon as possible to avoid flocculation of the barium which results in irregular mucosal coating.

No unpleasant reactions or side effects attributable to the carboxy-methylcellulose have been observed in more than 2,000 patients examined. Although several reports of hepatotoxic effects of tannic acid when used in high concentrations have appeared recently,[11,15] it is believed that the evidence available is insufficient to indict it when known low doses are used in barium enema studies.[7] In spite of this, we prefer to avoid the use of tannic acid in barium enema examinations or in the preparation of these patients.

We consider adequate preparation of the colon, good barium suspensions and high kilovoltage technique important in obtaining satisfactory barium enema examinations. In our experience, the roentgenograms of the barium filled colon, especially the compression spot roentgenograms, are more useful than postevacuation roentgenograms in the detection of polyps smaller than 1 cm. in diameter. This observation concurs with that of Steinbach and Burhenne,[18] but is different from the experience of Christie *et al.*[5] who detected 90 per cent of the polyps on postevacuation roentgenograms. However, when masses larger than 2 cm. are present, the postevacuation roentgenogram is very useful in demonstrating mucosal detail, contour of the lesion, presence of ulceration, etc.—macroscopic features that help assess the pathologic nature of the lesion.

SUMMARY

Laboratory tests were made to evlauate the viscosity, stability, settling properties, and adhesiveness of USP barium sulfate, barium suspensions with 0.2, 0.5 and 1.0 per cent carboxy-methylcellulose, and of barium suspensions with 0.25 per cent tannic acid added. The postevacuation roentgenograms of 1,000 barium enema examinations were compared, 200 examinations being performed with each of these 5 barium mixtures. The results show that 1.0 per cent carboxy-methylcellulose has a comparable stabilizing effect in barium suspensions and enhances mucosal coating equally as well as a 0.25 per cent concentration of tannic acid, without the possible undesirable toxic reactions of high concentrations of the latter, and that both are preferable to lower concentrations of carboxy-methylcellulose.

Further investigation is necessary to continue improving the suspension of barium mixtures.

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UNUSUAL COMPLICATION OF BARIUM STUDIES*

REPORT OF CASE OF ADHERENT CECAL BAROLITH

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IN SURVEYING the literature on complications of barium studies, one finds few recorded instances of barium inspissation in the colon. In fact, a recent, thorough review[47] of the complications of barium enema studies fails to mention this entity entirely.

Previously reported complications of barium studies of the gastrointestinal tract—besides problems with inspissation and retention of barium—have been reported with varying degrees of frequency and deserve brief mention here. Contamination of the peritoneal cavity or retroperitoneal space has occurred secondary to escape of barium through a peptic ulcer that was either previously perforated but undiagnosed[49] or perforated during or shortly after the time of fluoroscopy.[22] Contamination may result from bowel wall injury by enema tubes,[61] Bardex balloons in the rectum[35] or in colonic stomas,[2] proctoscopic examination,[25] biopsy,[23] and trauma.[44,61] Escape of barium also may occur because of pre-existing diseases such as carcinoma of the stomach[50] or colon,[25] mesenteric thrombosis,[61] adhesions,[61] perforated appendix with abscess,[28] irreducible intussusception (usually of more than 48 hours' duration),[36] amebiasis,[21] diverticulosis[61] and diverticulitis,[8,40] lymphopathia venereum,[61] chronic ulcerative colitis,[42] volvulus,[61] pelvic inflammatory disease,[61] chronic herniation or breakdown of a colonic stoma,[61] Hirschsprung's disease,[15] and postradiation sigmoiditis.[18] Spillage into the peritoneal cavity may result in adhesions[61] and spillage into the retroperitoneal space or other tissues may result in granuloma formation.[6,10,28,33] Such granulomas have been reported to cause ureteral obstruction.[14] Partial or intramural perforation of the colon has also been reported.[52]

The presence of incomplete obstruction of the small[9] or large[29] intestine may cause retention of barium and produce complete obstruction.

Hirschsprung's disease may also predispose the patient to water intoxication[24,27] and reflex cardiac inhibition[53] during barium enema examination. Water intoxication has also been reported in patients with only chronic constipation.[38]

The filling of other body systems during barium studies of the gastrointestinal tract may be regarded as being a diagnostic sign or a complication, depending on the circumstance. The urinary tract,[37] biliary tree,[20] bronchial tree,[46] and venous intravasation[43] (which have been reported to result in hepatic abscess[26]) have been filled by barium. Venous intravasation has also resulted from vaginal placement of a Bardex balloon with subsequent rupture of the vagina.[60] Sublethal venous intravasation has been postulated.[56]

Accidental overfilling during barium enema study has resulted in cecal rupture and retrograde flow, producing regurgitation and aspiration of barium.[12] Tracheal aspiration has also been reported during barium meal study.[55]

Barium sulfate itself is nontoxic but may become contaminated with other barium salts[32] or even be accidentally replaced with toxic barium carbonate[11] or bismuth compounds.[13] Contamination with photographic developer, causing death, has been reported.[34] Addition of tannic acid has been incriminated as a cause of toxicity.[30]

Patients with chronic ulcerative colitis have been thought to hemorrhage, either because of use of castor oil or stretching

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from the barium enema.[39] Toxic megacolon has been thought to be produced or made worse by barium enema.[31,51]

Emphysema from air escape has been reported during air contrast studies and also during barium enema without air studies.[5]

Radiation burns of the skin during gastrointestinal examinations have been reported as late as 1945.[16]

Electrocardiographic changes during barium enema study and even a fatal myocardial infarction have recently been reported.[3] Inability to control the movements of the patients, particularly children, can result in complications.[45] Transmission of enteric pathogens through use of contaminated enema apparatus has been postulated.[54]

In this paper, the only case of asymptomatic, adherent, nonobstructing, barium fecalith (barolith) encountered at the Mayo Clinic in the past 20 years is described.



Fig. 1. Roentgenogram after barium enema, June, 1963.

Report of a Case

The patient, a 63 year old housewife, had been seen at this clinic on several previous occasions since 1940 for various minor conditions. Her most recent previous examination here had been in 1963, when her chief complaint was indigestion and epigastric distress. In the course of that examination, roentgenographic studies of her colon showed normal findings (Fig. 1), but those of the stomach demonstrated a duodenal ulcer and a tiny, diaphragmatic hernia. Appropriate medication and a liberal ulcer diet were suggested.

When seen again in March, 1965, she complained of continuation of mild indigestion and also of a pain in the left lower quadrant of the abdomen, which had begun in November, 1964. At first, the pain had been sharp and had lasted 3 days; however, it had not been severe enough to interrupt her normal activities. This pain had recurred on several occasions but had not been nearly as severe as during the initial attack.

The results of a general physical examination and of a proctoscopic examination were normal. In the early part of the roentgenographic examination of the colon, a dense, foreign body was noted in the cecal region; when the examination was completed, the colon was considered to be normal, and the dense, foreign body was thought to be within the lumen of the cecum (Fig. 2*A*). This was believed to represent a barolith from her previous studies. She had had no barium studies in the intervening period.

The patient was encouraged to drink large amounts of fluids, eat roughage, and take enemas and laxatives daily for 1 week. At the end of this time a roentgenogram showed the barolith to be unchanged (Fig. 2*B*). She was advised to continue to drink 10 glasses of water each day and to take ½ ounce each of mineral oil and milk of magnesia daily; after 2 weeks, dioctyl sodium sulfosuccinate (Doxinate), 60 mg./day, was added to the regimen. However, after 1 month of this treatment, a roentgenogram revealed the barolith still unchanged. Surgical removal was advised.

At operation, gentle palpation through the cecal wall detected the barolith, and it was definitely anchored in position. An incision was made through the wall of the cecum; the barolith was found to be rather firmly attached to the mucosa. However, the mucosa was gently teased off the barolith, and removal was accomplished without difficulty. There was no abnormality of the cecum, but there was

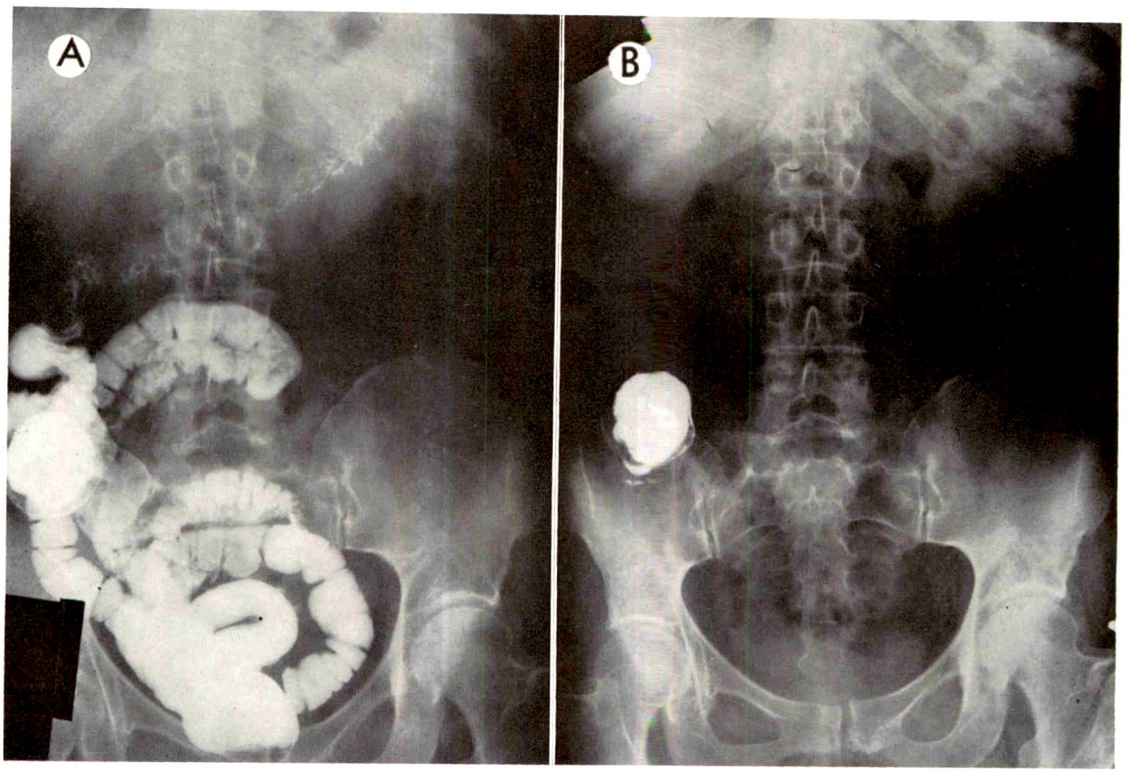


FIG. 2. (*A*) First observation of barolith in cecum, March, 1965. (*B*) Barolith unchanged 1 week later after daily enemas and laxatives and copious intake of fluids and roughage.

moderate inflammation in the cecal wall overlying the barolith. The barolith measured 4 cm. in diameter (Fig. 3, *A* and *B*).

DISCUSSION

The more frequent complications of barium enema studies were reviewed by Seaman and Wells[47] in 1965 and by Pyle and Samuel[41] in 1960. Infrequently mentioned in the literature is the less dramatic complication of retention of barium. Golob[17] reported 3 cases of retained barium, which were symptomatic but did not require surgical removal. In 1944, Banks[1] stated that hard, inspissated barium occurred in the rectum in 5 per cent of patients after gastrointestinal barium studies unless oil, a laxative, or an enema was given after the examination.

Valladares[57] coined the term "barolith" for inspissated barium associated with feces. He described 10 cases of obstructive problems secondary to diagnostic use of barium; only 2 of these cases were associated with pathologic conditions of the bowel. Of his 8 other cases, 4 occurred after small bowel studies and 4 after colon studies in patients with chronic constipation. He urged the use of laxatives or enemas or both after barium studies. In 1952, Serjeant and Raymond[48] reported a case of perforation of the sigmoid colon 20 hours after a barium meal study in a patient with no colonic lesion. They thought that inspissated barium in this dehydrated patient was a definite factor in causing the perforation. They also cited Kaulich who, in 1930, reported a case in which he thought that barium, which had become impacted in the sigmoid and caused obstruction, had also caused ulceration of the mucosa and led to rupture at the time of barium enema 27 days later.

In 1954, Gubler and Kukral[19] reported 4 cases of appendicitis occurring in patients who previously had had barium meal studies and in whom baroliths were found obstructing the lumen of the appendix.

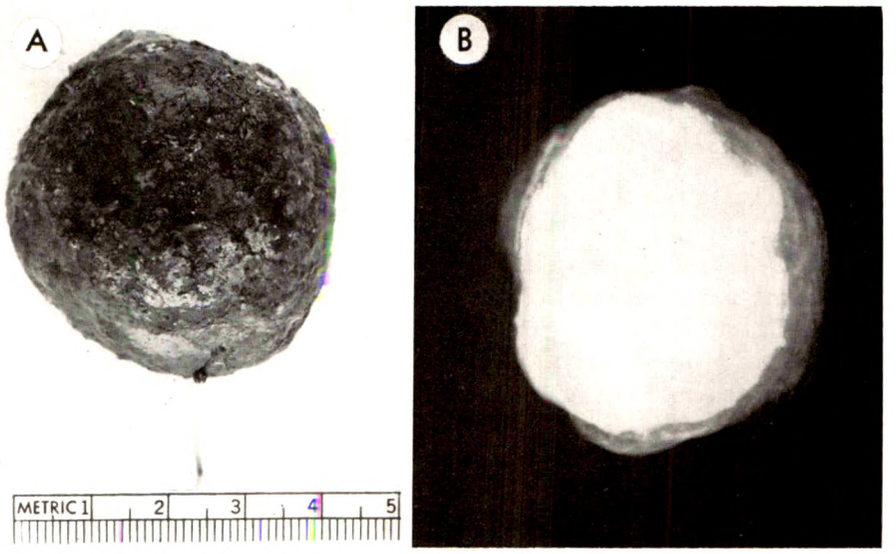


Fig. 3. Barolith. (*A*) Gross appearance. (*B*) Roentgenogram of the gross specimen showing central core of barium and surrounding rim of feces.

They recommended prophylactic removal of such baroliths. Young[59] suggested that patients should be warned if barium stayed in the appendix longer than 1 week and that prophylactic appendectomy should be done if it stayed longer than 4 weeks. Burrows[7] reported that he had seen barium persist in sigmoid diverticula for as long as 22 months after a barium enema.

In 1959, Borden and Hermel[4] reported 2 interesting cases of retained barium. One patient had semisolid, retained material in the distal limb of a loop colostomy, and the other had a solid, nonadherent barolith in the rectum, which had been present for 1 year after a barium meal study. In the latter, the barolith was freely movable and necessitated finger manipulation in order for the patient to have a bowel movement. Neither of these patients required surgical removal. Borden and Hermel[4] also studied 100 patients who had had various barium studies not followed by laxatives or enemas, and they found, by follow-up roentgenograms of the abdomen, that all barium in all patients was gone by the end of 4 weeks, except in 4 patients who had a small amount of retention in diverticula. Fifty-seven of the 100 were free of barium by 1 week. Prolonged retention in the right colon was noted only in women. No baroliths formed in these 100 patients. They recommended that a laxative or cleansing enemas or both be given to all patients after barium studies and that senile patients and patients with constipation should have especially careful follow-up.

The addition of asymptomatic, adherent, nonobstructing barolith to the already long list of complications of barium studies may seem inconsequential, but we think that, because of the possibilities of intussusception, obstruction, ulceration, or perforation, these foreign bodies are significant and should be surgically removed. Surgical removal without excessive medical purging is also indicated because, in our case, medical treatment was unsuccessful. Walker,[58] in 1948, reported 2 similar cases except that they were not associated with the use barium. He also recommended surgical removal of the mass.

It is difficult to say whether retention of barium is more likely to occur after a barium meal or after a barium enema. In our case, the patient had had both studies. Certainly, such factors as bowel motility, cecal stasis, hydration of the patient, physical characteristics of the barium preparation (including additives), use of oil or

laxatives or both before or after examination, and the presence of pathologic conditions in the bowel may affect the retention of barium.

SUMMARY

A case of asymptomatic, adherent, nonobstructing, barium fecalith (barolith) of the cecum, present for 2 years after previous barium studies, in a 63 year old woman is reported. Although obstruction by retained barium has been described, this is the first report of this type of complication of barium studies. Surgical removal of such fecaliths is recommended because of their adherence and resistance to purging as well as the possibilities of intussusception, obstruction, ulceration, or perforation of the colon.

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APPENDICITIS: "FUNCTIONAL" BOWEL OBSTRUCTION ASSOCIATED WITH PERFORATION OF THE APPENDIX*

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WE HAVE previously reported instances of bowel distention simulating obstruction in the absence of an organic mechanical cause postulating a relationship to autonomic nervous system imbalance.[3] Cases of "functional" ileus have been reported in a variety of pathologic states—one of them being appendicitis with perforation. Herein reported are 6 cases of perforated appendix where bowel distention could be mistaken for mechanical obstruction—where the underlying condition is masked by significant bowel dilatation. In none of these cases was there mechanical block of the intestinal tract.

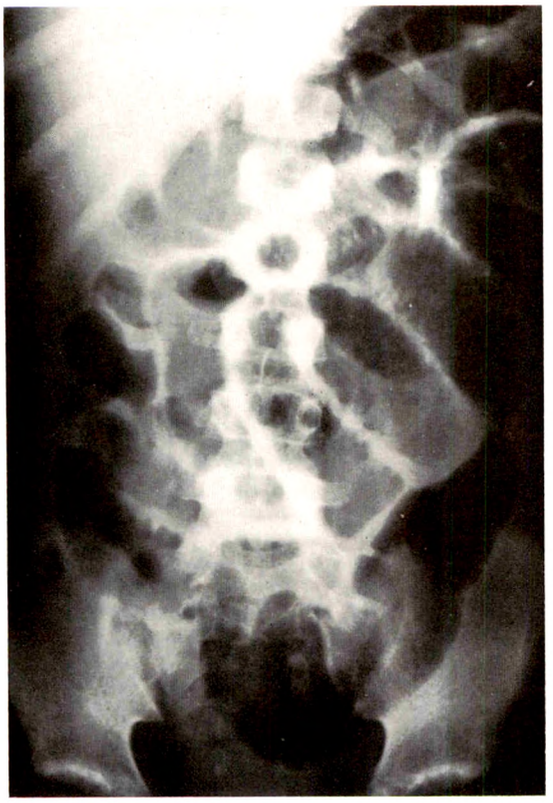


FIG. 1. Case 1. Roentgenogram of a 7 year old patient with perforation of the appendix. Considerable bowel distention, primarily of the small bowel, questionable air in abscess zone, and exudate between the dilated bowel loops.

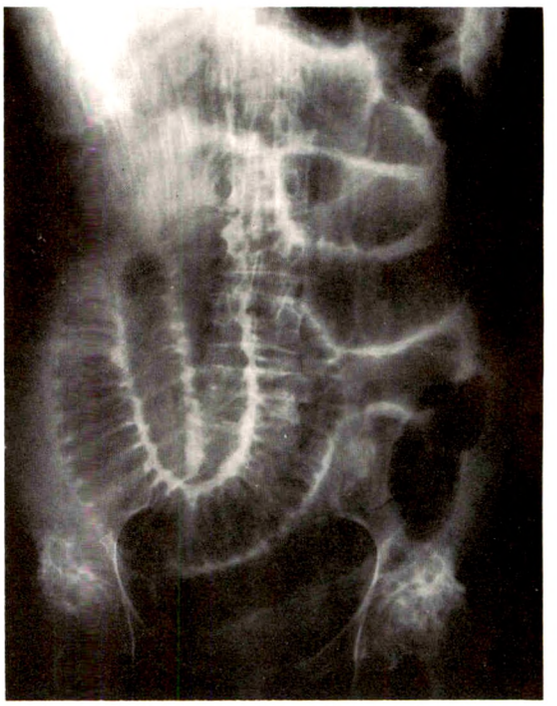


FIG. 2. Case 11. Roentgenogram of a 70 year old patient. Gangrenous, ruptured retrocecal appendix. Marked small bowel distention with the appearance of mechanical obstruction.

REPORT OF CASES

CASE 1. A. C. was a 7 year old white male with a 5 day history of abdominal pain. A roentgenogram of the abdomen (Fig. 1) showed considerable bowel distention, particularly of

* From the X-ray Departments of Grant Hospital of Chicago, Chicago, Illinois; Lake Forest Hospital, Lake Forest, Illinois; Research and Educational Hospitals of the University of Illinois College of Medicine, Cook County Hospital, Chicago, Illinois.

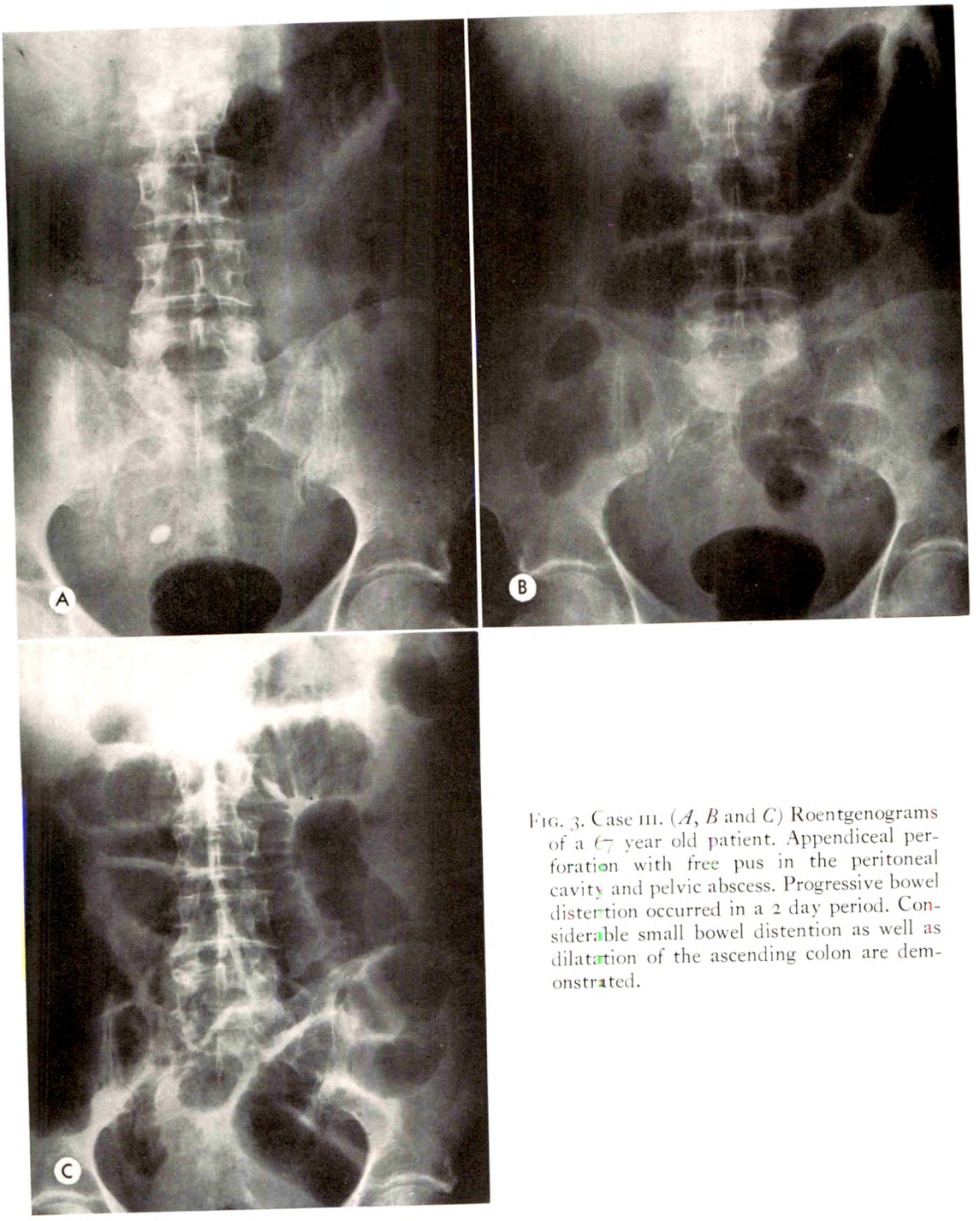


Fig. 3. Case III. (*A*, *B* and *C*) Roentgenograms of a 67 year old patient. Appendiceal perforation with free pus in the peritoneal cavity and pelvic abscess. Progressive bowel distention occurred in a 2 day period. Considerable small bowel distention as well as dilatation of the ascending colon are demonstrated.

the small bowel with evidence of exudate between bowel loops. At surgery, there was a perforation along the lateral aspect of the appendix and considerable free pus was present in the right lower quadrant of the abdomen as well as in the pelvic cavity.

Case II. E. F. was a 70 year old white female with a 5 day history of abdominal pain and distention. A roentgenogram (Fig. 2) demonstrated marked small bowel distention compatible with small bowel obstruction. Extensive degenerative hip disease was also present.

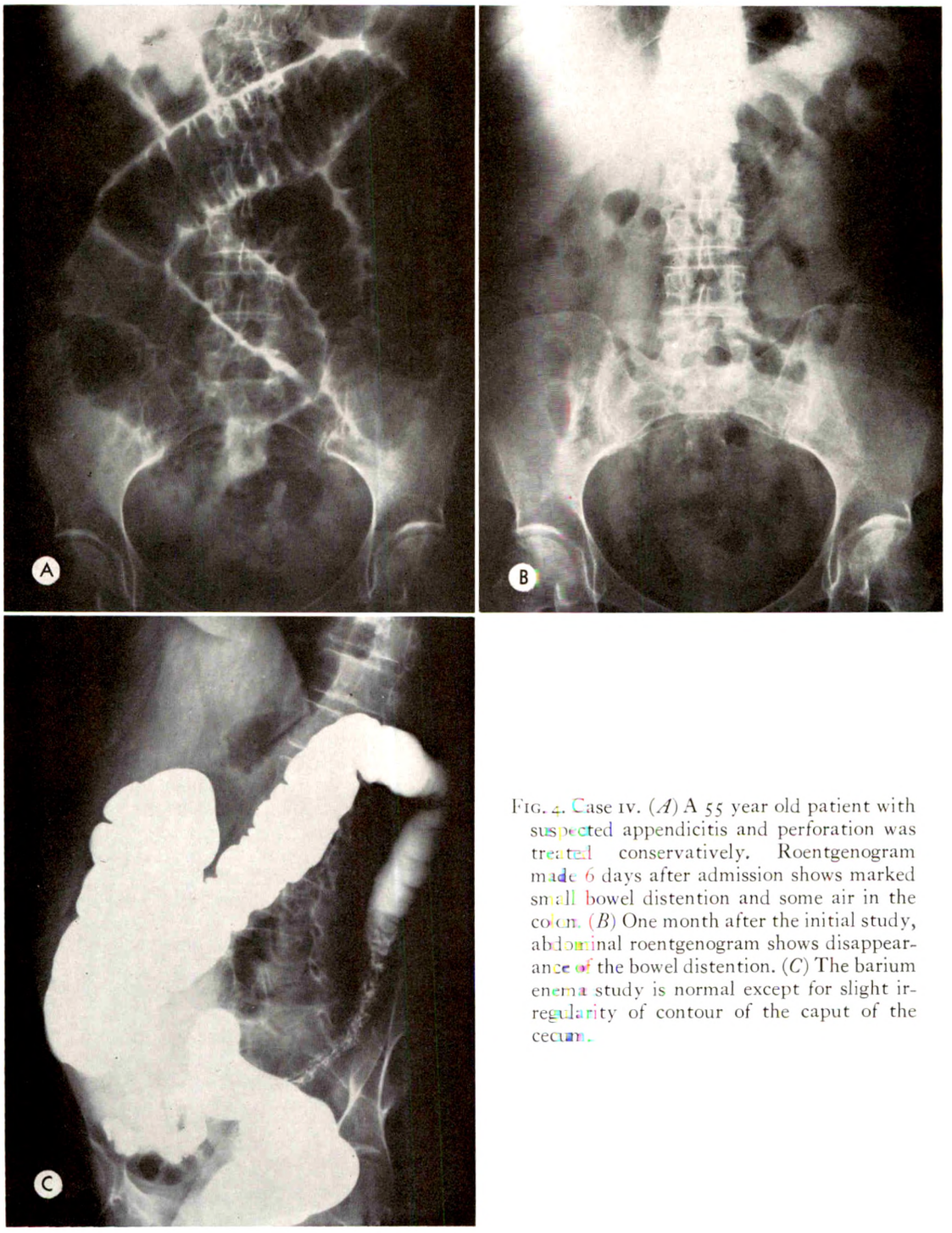


FIG. 4. Case IV. (*A*) A 55 year old patient with suspected appendicitis and perforation was treated conservatively. Roentgenogram made 6 days after admission shows marked small bowel distention and some air in the colon. (*B*) One month after the initial study, abdominal roentgenogram shows disappearance of the bowel distention. (*C*) The barium enema study is normal except for slight irregularity of contour of the caput of the cecum.

At surgery, a ruptured and completely gangrenous appendix was found in retrocecal position.

CASE III. L. W., a 67 year old white male, had a 1 day history of abdominal pain and generalized abdominal tenderness as well as signs of cardiac disease with auricular fibrillation. Abdominal roentgenograms (Fig. 3, *A*, *B* and *C*) made within a 2 day period showed progressive bowel distention involving primarily the small bowel and, to a lesser extent, the colon.

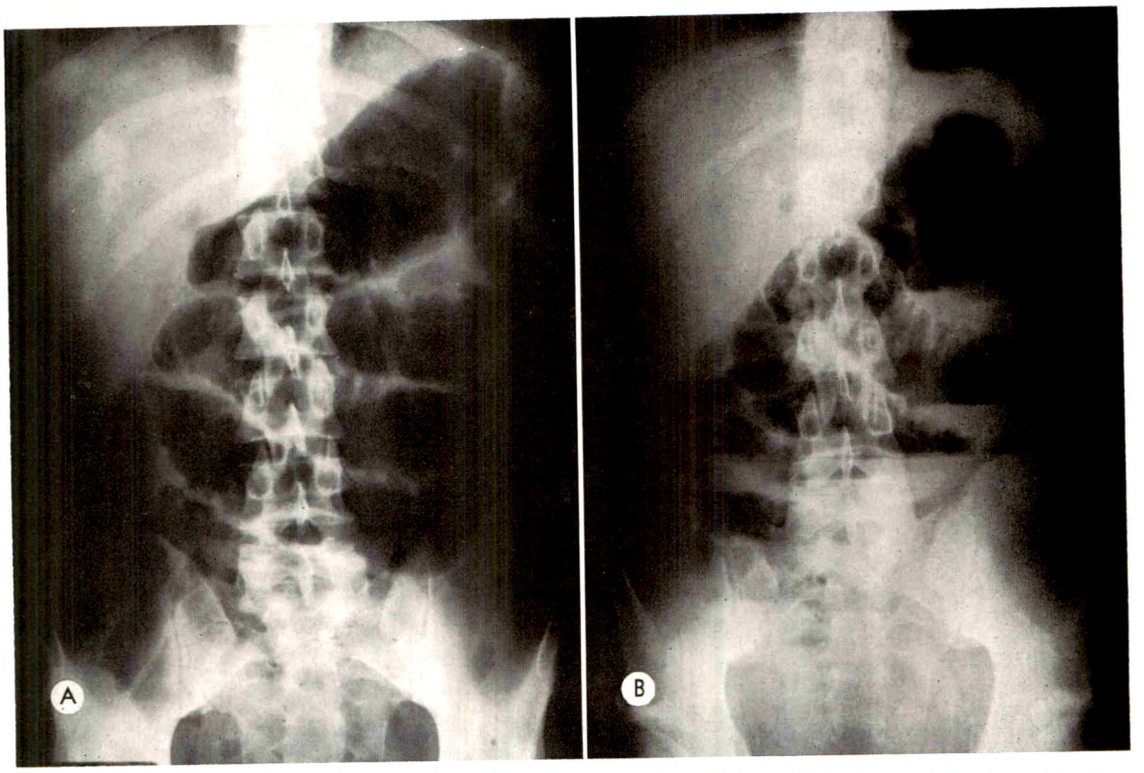


Fig. 5. Case v. (*A* and *B*) Roentgenogram of a 21 year old patient. Retrocecal perforated gangrenous appendix. Marked small bowel distention with numerous air-fluid levels simulating mechanical obstruction is demonstrated.

At surgery, free pus was noted in the abdomen. The appendix dipped into the pelvis with a perforation in the mid-portion. A fairly large pelvic abscess was present.

Case iv. E. G., a 55 year old white female, had a 1 day history of severe lower abdominal pain and lower abdomen tenderness, especially on the right. A perforated appendix was suspected clinically. Bowel distention occurred 3 days after admission and a roentgenogram of the abdomen 6 days after admission (Fig. 4*A*) demonstrated marked bowel distention, particularly of the small bowel. Treatment was conservative.

The patient was readmitted approximately 1 month later for surgery. A small mass was palpable in the right lower quadrant of the abdomen. An abdominal roentgenogram (Fig. 4*B*) and a barium enema examination (Fig. 4*C*) showed disappearance of bowel distention and slight irregularity of the contour of the caput of the cecum. At surgery, new adhesions involving the cecum, appendiceal area, and terminal ileum were found as well as a perforated appendix. There was a free fecalith in the peritoneal cavity. No free pus was encountered.

Case v. P. L., a 21 year old white male student, had a 5 day history of abdominal pain, which he ignored since he was pre-occupied with examinations. A physician treated him with antibiotics but pain and vomiting continued. The patient became toxic with elevated temperature. On admission to the hospital, there was marked generalized tenderness and rigidity of the abdomen. No mass was palpated. Clinical diagnosis was perforated appendix.

Abdominal roentgenograms (Fig. 5, *A* and *B*) demonstrated considerable small bowel distention with air-fluid levels.

At surgery, an acute suppurative process was found when the peritoneal cavity was entered. Further exploration revealed a retrocecal perforated gangrenous appendix. A large collection of purulent material was present in the hollow of the pelvis.

Case vi. G. R., a 57 year old white male experienced sharp abdominal pain of 2 days'

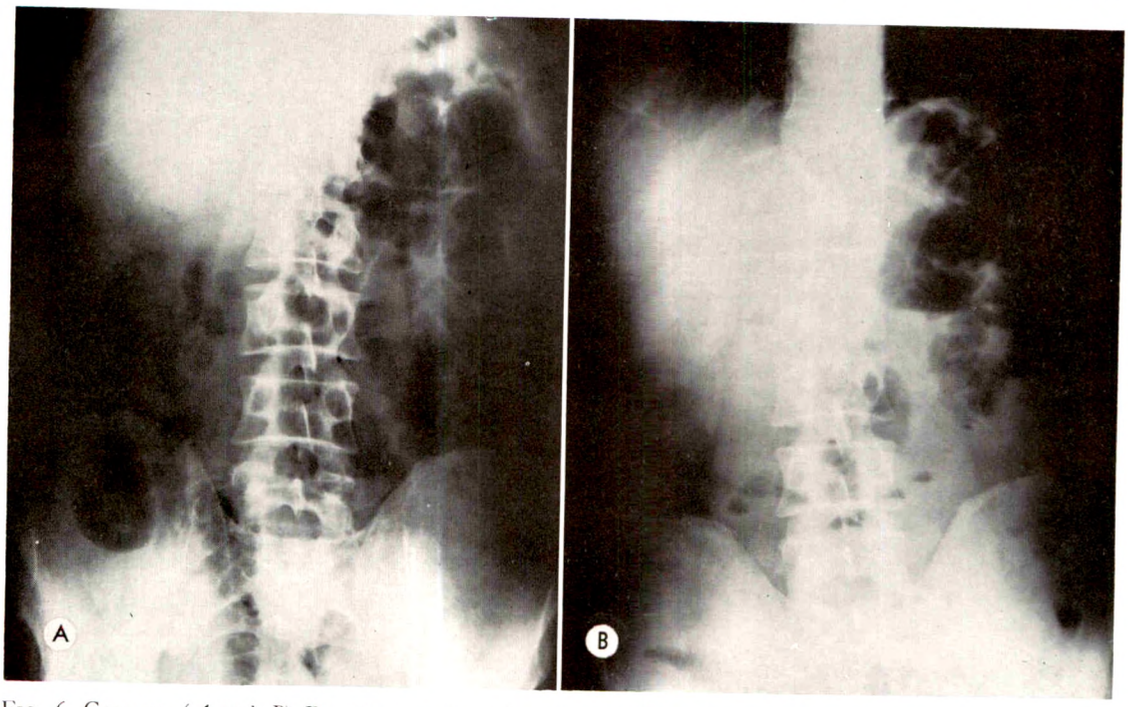


FIG. 6. Case VI. (*A* and *B*) Roentgenograms of a 57 year old patient. Perforated gangrenous appendix. Slightly distended small bowel loops with air-fluid levels in the left upper quadrant of the abdomen are demonstrated. There is possible calcification or a pill overlying the sacrum.

duration. Physical examination revealed abdominal distention with marked lower abdominal tenderness and guarding. The clinical impression was that of acute appendicitis.

Roentgenograms of the abdomen (Fig. 6, *A* and *B*) taken the day after admission demonstrated slightly distended loops of small bowel with air-fluid levels, primarily in the left upper abdomen. Either a calcification or a pill was seen overlying the sacrum.

At surgery, a perforated gangrenous appendix was noted in the hollow of the pelvis which had produced generalized peritonitis. A fecalith was present within the lumen of the perforated appendix.

DISCUSSION

Bowel distention in association with appendicitis has been previously reported[1, 2,4,5,6] and can manifest itself as local right sided ileus or more general bowel distention. Our interest in this subject concerns primarily its inclusion in the group of disease syndromes which manifest themselves as "functional obstructions."

We have previously listed some considerations for etiologic factors in functional ileus.[3] Cases of appendiceal perforation can be classified with other peritoneal irritation syndromes which initiate inhibitory sympathetic nervous system response and bowel dilatation.

SUMMARY

1. Appendicitis with perforation can be associated with "functional bowel obstruction."

2. Bowel distention, when present, can relate to strong sympathetic (thoracolumbar) nervous system stimulus.

3. Six cases of perforated appendix with significant bowel distention are herein reported.

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THE THERAPEUTIC ACTION OF ORAL HYPAQUE IN BOWEL OBSTRUCTION

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IN THE past 3 years numerous patients have been admitted to the Veterans Administration Hospital, Phoenix, Arizona, who were treated both medically and surgically for bowel obstruction due to various causes. The majority of these patients are in the older age group and are in relatively poor condition by the time they reach this Hospital.

Since the advent of the use of oral hypaque in the study of bowel obstruction cases, this mode of examination has been used with increasing frequency. In quite a few such cases we have noted that a few hours after peroral (usually by gastric tube) administration of 100 cc. of 40 per cent hypaque the patient experiences a large, mostly liquid, bowel movement with subsequent alleviation of his complaints and improvement of objective findings. Some of these cases are reported below.

REPORT OF CASES

CASE I. (Fig. 1, *A*, *B* and *C*) H. B., a white male 66 years of age, presented a history of a skin melanoma which was removed in 1961. He was admitted on February 15, 1963 with a diagnosis of hemiplegia and postoperative removal of a skin melanoma with widespread metastases. Roentgenographic examination of the abdomen on February 20, 1963 showed marked dilatation of the small bowel with gas and fluid levels. The obstruction, when compared with that on a previous roentgenogram dated February 13, 1963, had shown progression.

On March 5, 1963 oral hypaque was administered into the stomach via gastric tube. Following this, the patient passed a large liquid brownish-red stool. On March 6, 1963 the hypaque was seen on a roentgenogram of the abdomen to be in the large bowel and there was considerable improvement, although not complete, of the small bowel distention. On March 8, 1963, the patient was taken to surgery and a small bowel obstruction due to a large metastatic melanoma was found. The tumor caused some intussusception at the site of obstruction. At surgery this tumor and obstruction were removed. Following the operation the patient improved and was discharged on March 22, 1963 in good condition.

On April 15, 1963, the patient's mental condition worsened, he became dull, gradually deteriorated, and expired on May 2, 1963. Autopsy showed widespread metastatic melanoma to the brain, lungs, mesentery and small bowel.

CASE II. (Fig. 2, *A*, *B* and *C*) T. C., a 64 year old white male, was admitted on July 31, 1965 with a diagnosis of an acute abdomen. Surgical exploration revealed an apparent appendiceal abscess. Following the operation abdominal distention and small bowel ileus occurred. The patient became progressively worse. No gas or stool was passed per rectum. On August 17, 1965 an upper gastrointestinal series was done with hypaque administered into the stomach via gastric tube. Within 2 hours, copious liquid bowel movements were initiated and occurred for several days.

Following this study, the patient experienced slow progressive improvement. For several days copious amounts of liquid brownish stools were passed. Gradually, the stools returned to normal and the patient was discharged in good condition on October 25, 1965.

CASE III. J. S. M., a 65 year old white male, was admitted on May 7, 1964 with complaints of abdominal discomfort and vomiting for 8 hours. The patient had a previous similar episode in 1962 which was relieved by decompression. His history revealed multiple abdominal surgical procedures, including a gastric resection in 1952. He had been repeatedly hospitalized at other institutions for recurrent small bowel obstructions. The physical examination was essentially negative except for diffuse tenderness. The small bowel sounds were tinkling and hyperactive. Roentgenograms of the abdomen with a Miller-Abbott tube in the stomach showed small bubbles of gas in the

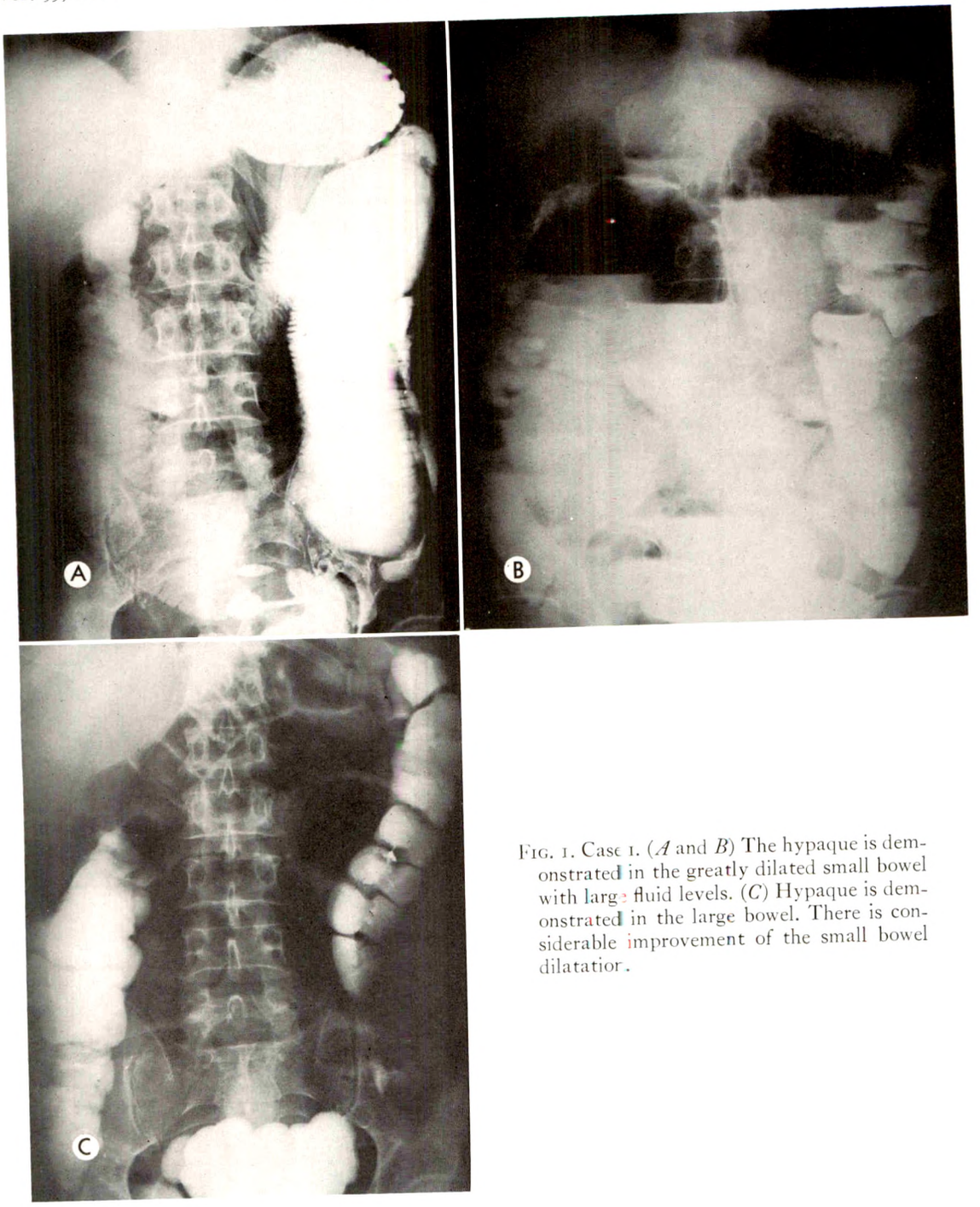


Fig. 1. Case 1. (*A* and *B*) The hypaque is demonstrated in the greatly dilated small bowel with large fluid levels. (*C*) Hypaque is demonstrated in the large bowel. There is considerable improvement of the small bowel dilatation.

terminal ileum, also some gas in the colon and rectum. There was a possibility of a very mild partial bowel obstruction but the findings were not definite. Subsequently, the Cantor tube passed into the small bowel very rapidly. On May 8, 1964 oral hypaque studies were done which showed rapid passage in 2 hours, the hypaque reaching the distal descending colon in 4 hours. Almost immediately, there was reported a large copious brown liquid stool. The patient had an uneventful recovery and was discharged on May 15, 1964 in good condition.

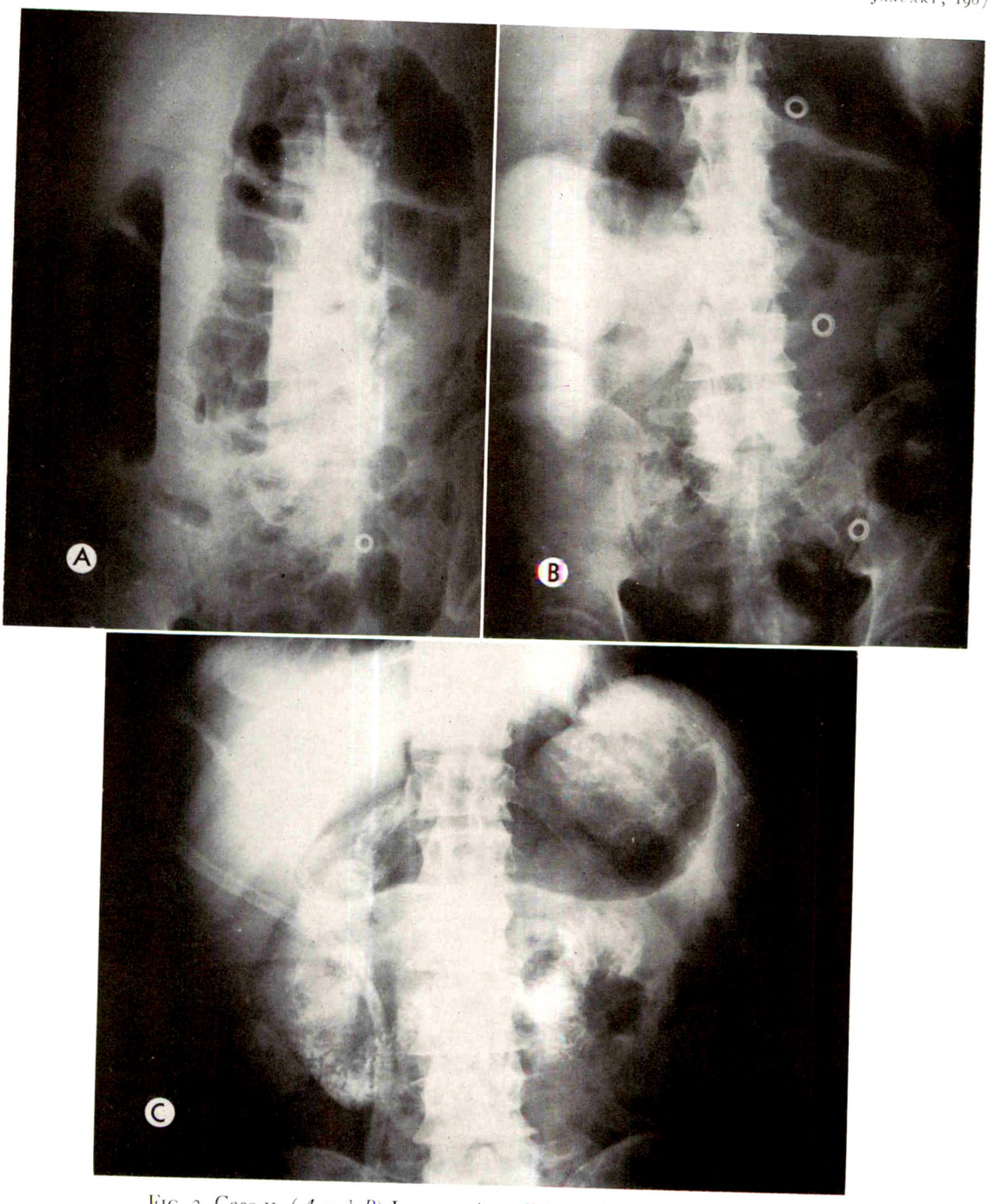


FIG. 2. Case II. (*A* and *B*) Large and small bowel ileus with fluid level. (*C*) Later hypaque study shows improvement.

CASE IV. L. H. C., a white male aged 67 years, was operated on December 17, 1962, for removal of a transitional cell carcinoma of the bladder. Postoperatively, the patient became progressively distended, which persisted in spite of the use of gastric and Levine tubes. He was re-operated on December 25, 1962, and a small loop of bowel herniating into the peritoneal floor of the pelvis was identified. This was released; however, the obstruction persisted. On December 26, 1962 oral hypaque studies were done which showed evidences of

small bowel dilatation and apparent partial mechanical obstruction. Shortly thereafter the patient passed gas and a liquid stool, and on December 28, 1962, it was evident that the obstruction and ileus were markedly improved. Although a complicating peritonitis and orchitis occurred, the patient showed gradual improvement and the ileo-bladder functioned well. He was discharged in good condition on January 23, 1963.

Case v. (Fig. 3) T. G., a white male aged 32 years, entered the Veterans Administration Hospital on August 23, 1965 with upper abdominal pains and an admission diagnosis of possible ruptured duodenal ulcer. On August 24, 1965 upper gastrointestinal hypaque studies were done via gastric tube; in 2 hours the hypaque was in the colon. No abnormalities of the small bowel were seen. A laparotomy was performed and an acute pancreatitis was found. There was no massive bowel movement after this examination and no gastrointestinal upset. The patient was doing well until September 2, 1965 when, after coughing, a rupture of the incision occurred which required additional surgery. Following this, he made a gradual recovery and was discharged in good condition on September 30, 1965.

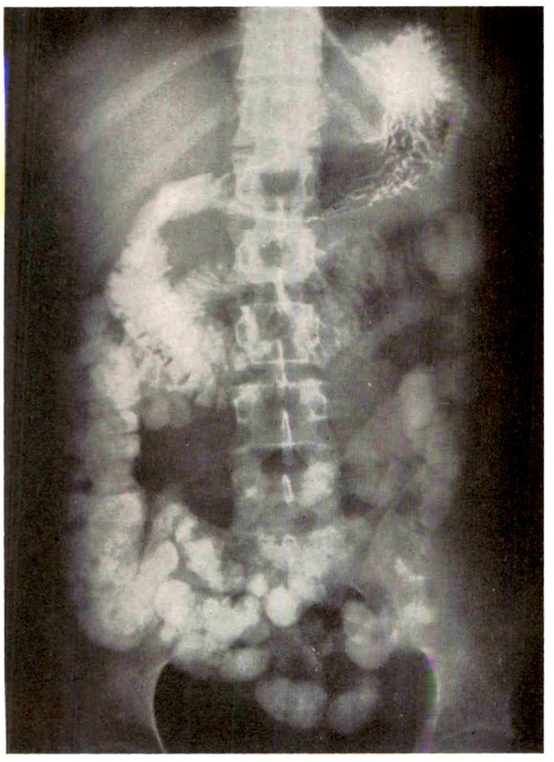


Fig. 3. Case v. A normal hypaque gastrointestinal study in a case of acute pancreatitis.

Comment. This case is presented to show that, if there is no partial or complete obstruction with considerable retained fluid in the bowel, the hypaque apparently does not cause massive bowel evacuations as described in previous cases. On the roentgenogram, hypaque was seen in the stomach and small bowel and in the colon in 2 hours. No evidence of small bowel obstruction or other particular abnormality was noted. There may have been a prominence of the duodenal loop, suggesting the pancreatitis found at surgery.

DISCUSSION

It is recognized that the cases presented do not have adequate control studies to rule out the obvious possibility of improvement with only intubation and time. However, our collective experience has indicated to us that there is a definite action of oral hypaque in the alleviation of small bowel obstruction. The chemistry or reasons for this are unknown to us.

SUMMARY

We have observed in many cases of mechanical bowel obstruction, an alleviation of that obstruction with the oral hypaque small bowel study. We feel that it is a worthwhile procedure in cases where the patient's general condition excludes immediate surgical intervention.

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The author is indebted to Dr. Leo Reich, Chief of the Radiology Service, Veterans Administration Hospital, Phoenix, Arizona, for the radiologic evaluation and follow-up of these cases; and to Dr. Hyman Lieber, Chief of Surgical Service, Veterans Administration Hospital, Phoenix, Arizona, for the clinical and surgical evaluation and management.

METASTATIC TUMOR TO THE SMALL BOWEL*

THREE CASES SIMULATING PRIMARY MALIGNANT TUMORS

By NORMAN L. POTESHMAN, M.D.
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NEOPLASM metastatic to the small bowel is rare and, because of its infrequent occurrence, can be mistaken for primary malignancy (carcinoma or lymphoma). DeCastro *et al.*,[1] in a review of material from the Mayo Clinic for the years 1905–1954, found 26 cases of metastatic involvement of the small bowel, excluding those associated with widespread peritoneal invasion or carcinomatosis and excluding involvement by direct extension. This number compares with 659 cases of primary small bowel tumors reported by Good[2] from the Mayo Clinic for the period 1938–1957.

Metastatic squamous cell carcinomas mimicking primary small bowel tumors occur most commonly from primary carcinoma of the cervix uteri. The kidneys are the most common primary site for adenocarcinoma metastatic to the small bowel with the gastrointestinal tract and ovaries contributing a smaller percentage. Malignant melanoma metastatic to the small bowel usually is primary in the skin; metastatic melanoma may present with central ulceration or umbilication, resulting in a so-called "bull's eye" or "target" lesion.[3]

Three interesting cases have presented at The University of Chicago Clinics which could have been diagnosed as primary malignant neoplasms in the small bowel on roentgen evidence alone; in fact, 2 of the 3 cases were so considered.

REPORT OF CASES

CASE I. This male, aged 66 years, presented with a history of two dizzy spells during the prior month with episodes of light-headedness, weakness and sweating lasting fifteen minutes. He also noted belching, indigestion and heartburn. Significant past history was a right nephrectomy 15 years previously for renal carcinoma, with invasion of renal veins found in the specimen. Stools were tested and found to be 4+ for blood by benzidine test. Gastroduodenal examination (Fig. 1, *A* and *B*) showed a large polypoid mass with a suggestion of an ulcer crater occupying the distal portion of the duodenal bulb and proximal portion of the descending duodenum. The history of hypernephroma was not given to the radiologist and diagnostic possibilities considered were polyp or smooth muscle tumor. Exploratory laparotomy revealed a large mass (Fig. 1*C*) involving the first and second portions of the duodenum and also the head of the pancreas. The tumor mass was very vascular and friable. Excision was attempted but the patient expired at surgery. Pathologic examination revealed a hypernephroid carcinoma consisting of typical clear cells entirely similar to that removed 15 years earlier. Autopsy disclosed no other sites of metastases. It is interesting that the patient had been asymptomatic during the 15 year interval.

CASE II. This male, aged 43 years, presented with a 6 month history of periumbilical abdominal pain and tenderness associated with nausea. He had noted a lump in the right axilla for 2 years. Gastroduodenal and small bowel examinations showed multiple polypoid masses in the stomach and small bowel (Fig. 2, *A*, *B* and *C*). Lymphoma was considered the most likely cause. Gastroscopy revealed multiple circular, raised, rounded lesions, varying in size from 2 mm. to 2 cm. and in color from gray to black. Biopsy revealed infiltrates of deeply pigmented cells. Dark brown, nonrefractile, coarse particles were present in the cytoplasm with considerable pleomorphism in the nuclei. A diagnosis of metastatic melanoma was made. Excision of the right axillary lymph node also revealed metastatic malignant melanoma. Careful re-examination of the skin and retinae was performed but a primary site could not be found. The patient's condition worsened rapidly and he expired 3 months later. Autopsy was not performed.

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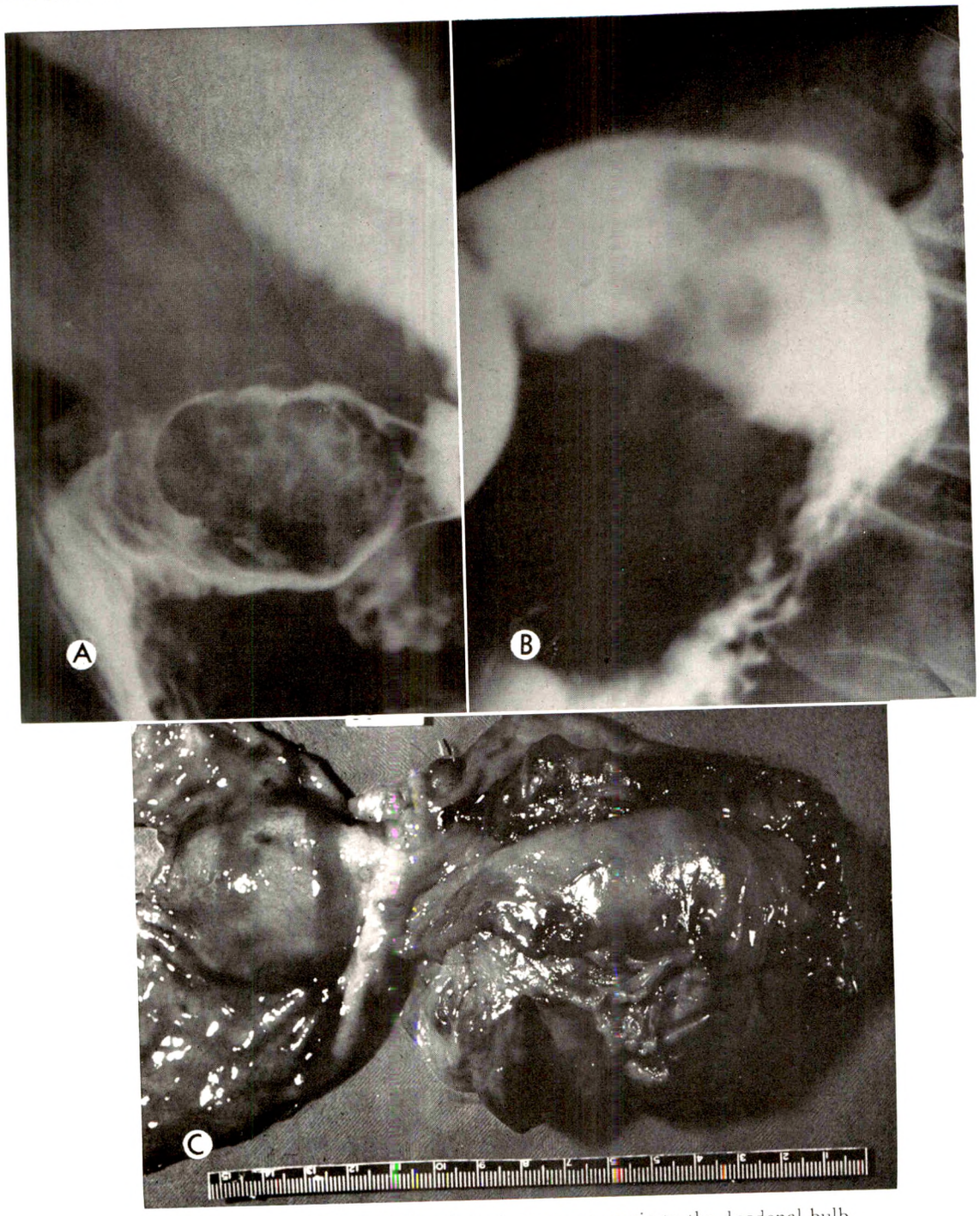


Fig. 1. Case 1. (*A* and *B*) Renal carcinoma metastatic to the duodenal bulb. (*C*) Surgical specimen showing polypoid mass in duodenum.

Case III. This male, aged 42 years, presented with a 6 month history of sharp pain in his left shoulder radiating to his elbow and hand. Numbness and weakness were noted. A diagnosis of arthritis had been made and symptomatic treatment was given. He began to note pain in the left side of the neck, and a left supraclavicular mass appeared. Biopsy of this lymph node

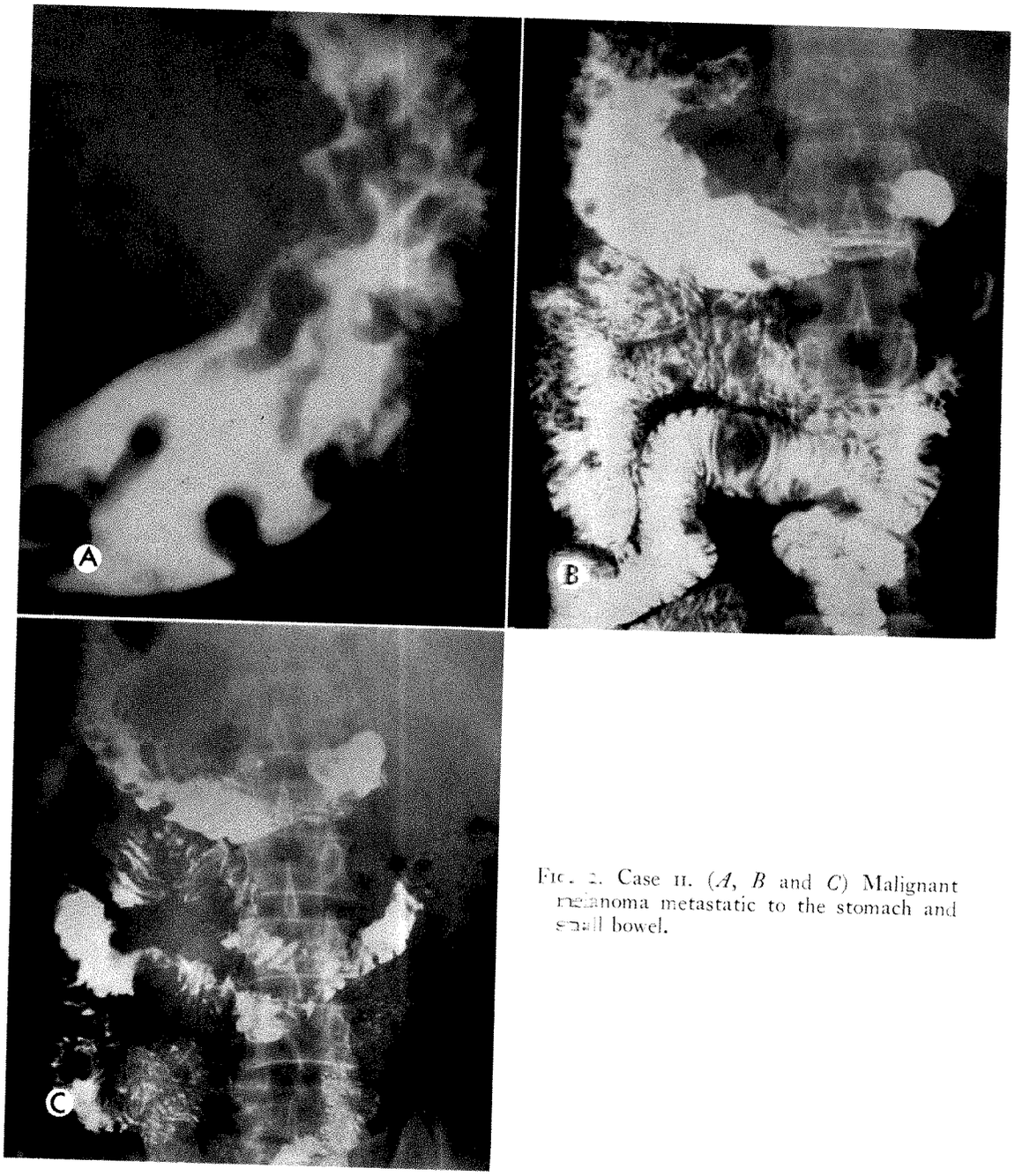


FIG. 2. Case II. (*A*, *B* and *C*) Malignant melanoma metastatic to the stomach and small bowel.

demonstrated squamous cell carcinoma. He was referred to The University of Chicago for radiation therapy. Examination revealed meiosis and ptosis on the left, a nontender, firm, fixed, supraclavicular mass and impaired percussion note and tactile fremitus over the left lung apex. A chest roentgenogram showed a homogeneous density in the apex of the left lung and a mass in the left hilus (Fig. 3*A*). Radiation therapy was given—6,182 rads were delivered to the left upper lung and 5,856 rads to the left hilus in 42 elapsed days through opposing anterior and posterior portals, using the 2 mev. Van de Graaff generator. The patient did well for 3 months when he began to note epigastric pain and generalized weakness, vomiting and tarry stools. Examination revealed tenderness and a mass in the left lower abdominal qua-

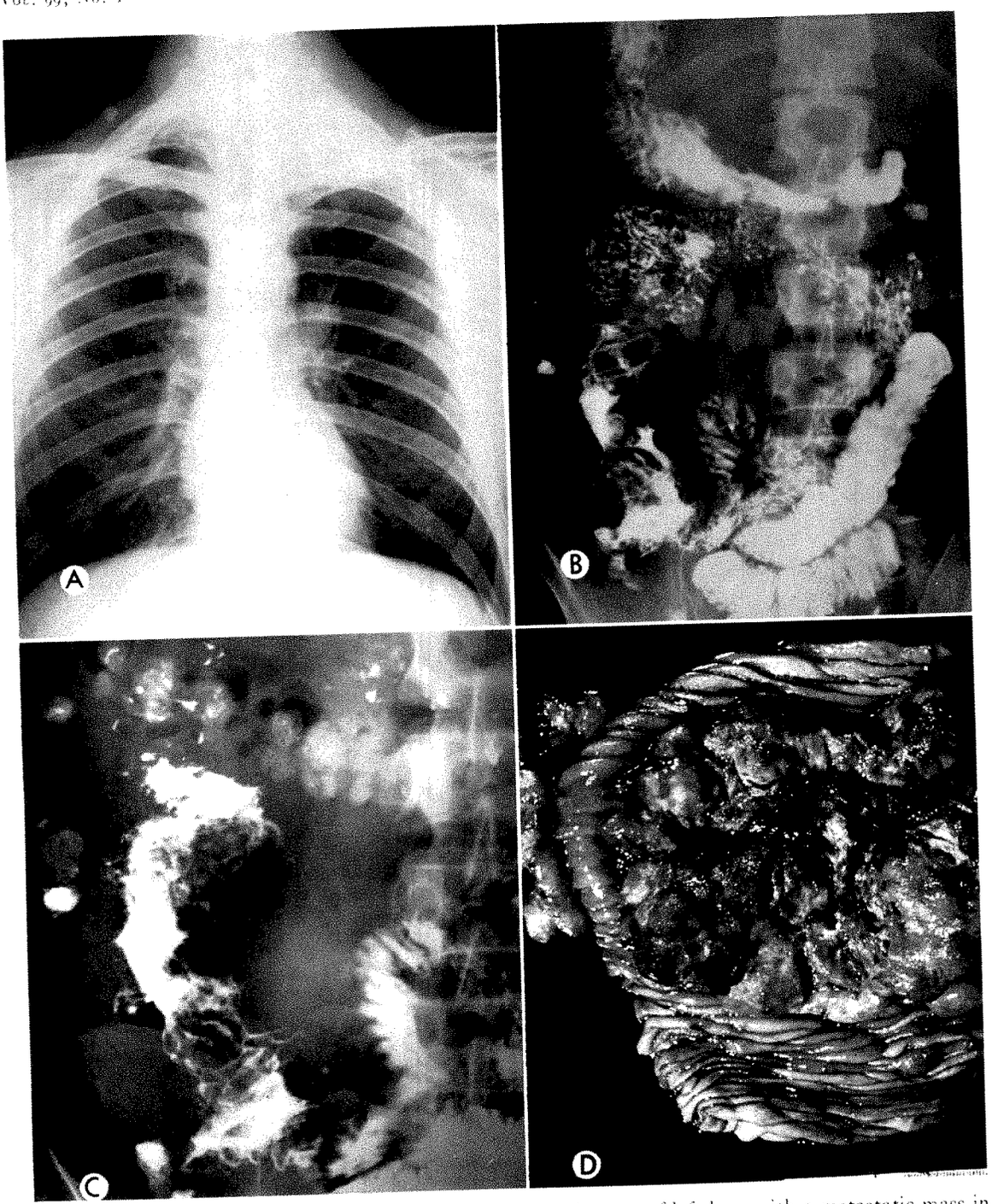


FIG. 3. Case III. (*A*) Bronchogenic squamous cell carcinoma in apex of left lung with a metastatic mass in the left hilus. (*B* and *C*) Metastatic lesion in the jejunum. (*D*) Surgical specimen showing fungating ulcerated mass.

drant. Small bowel examination showed a large ulcerated lesion in the jejunum with several intraluminal masses (Fig. 3, *B* and *C*). A palliative resection was performed and the pathologic specimen (Fig. 3*D*) showed a large fungating tumor mass with ulceration and necrosis, which

histologically represented metastatic squamous cell carcinoma. The patient expired 7 months later.

DISCUSSION

In the first case, due to inadequate clinical history, and in the second case, due to an occult primary lesion, the diagnosis of metastatic involvement of the small bowel was not considered. In the third case, it was stated frankly that without the history of bronchogenic carcinoma the roentgenographic findings would have been diagnosed as lymphoma. These cases indicate the necessity for including metastatic carcinoma in the differential diagnosis of small bowel tumors even if a primary lesion is not known.

SUMMARY

Three cases of metastatic involvement of the small bowel simulating primary malignancy are reported. These were proven to represent metastatic disease from the kidney, the lung and metastatic melanoma from an occult primary lesion. An index of suspicion of metastatic involvement should be maintained when small bowel tumors are demonstrated.

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VOL. 99, NO. 1

NONANGIOGRAPHIC MANIFESTATIONS OF INTESTINAL VASCULAR DISEASE

By J. DAVID DUNBAR, M.D.,* *and* SIDNEY W. NELSON, M.D.†
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THE interest in vascular and hematologic diseases which produce intestinal ischemia or intramural hemorrhage has increased rapidly during the last 10 years as the diagnostic criteria for their identification have improved. The advent of safe and frequent angiographic studies has also resulted in a marked improvement in the correlation between disease of the visceral branches of the abdominal aorta and their clinical manifestations, and has led to further refinements in the diagnosis of these diseases by clinical and routine roentgenologic methods. It should be emphasized, however, that routine plain film studies of the abdomen and positive contrast studies of the small bowel and colon can result in accurate diagnosis which can often preclude the need for more complex angiographic or surgical procedures. Furthermore, the correct interpretation of these routine roentgenographic studies can be of great value in the proper selection of those patients requiring further angiographic or surgical studies. Therefore, it is our purpose in this paper to review the interesting and varied spectrum of diagnostic criteria as seen on these conventional roentgenographic studies.

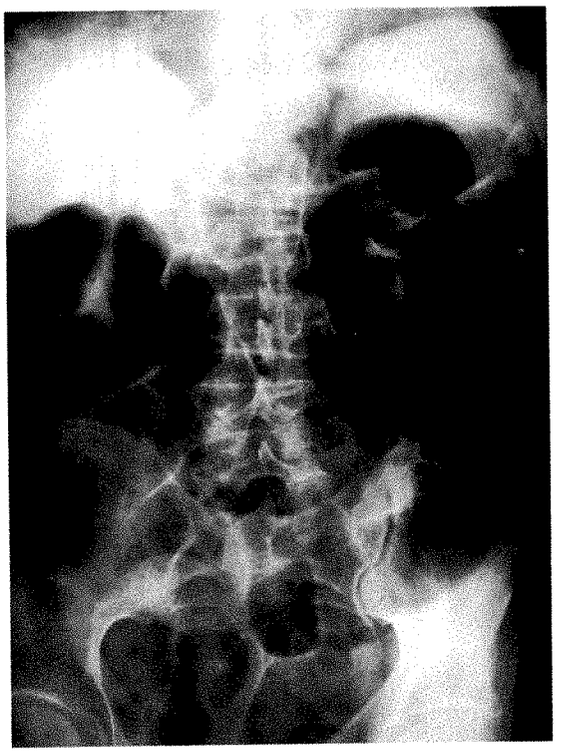


FIG. 1. Abdominal roentgenogram of a 74 year old man who entered University Hospital with a 2 week history of mild abdominal pain and 3 days of severe abdominal pain, nausea and anorexia. There is marked distention of the small intestine and colon extending to the hepatic flexure. Exploratory laparotomy was performed and the entire small bowel was found to be infarcted. He expired on the first postoperative day.

EVIDENCE OF INTESTINAL VASCULAR DISEASE AS SEEN ON PLAIN ROENTGENOGRAMS OF THE ABDOMEN

Roentgenograms of the abdomen made in the supine and erect positions are often helpful in the evaluation of patients with extensive thrombosis of mesenteric veins or thrombo-embolic disease of the mesenteric arteries. In order to understand the roentgenologic abnormalities, it is helpful to keep in mind the pathologic physiology. Acute occlusion of a mesenteric artery is first followed by a rippled, blanched appearance of the intestine with contracted arterioles and venules and some small scattered bluish spots due to capillary pooling. Three to 4 hours later, as the arteriolar muscle becomes fatigued, larger bluish areas appear between the pale areas. Finally, after 4 to 8 hours general loss of arteriolar muscle tone and integrity of the

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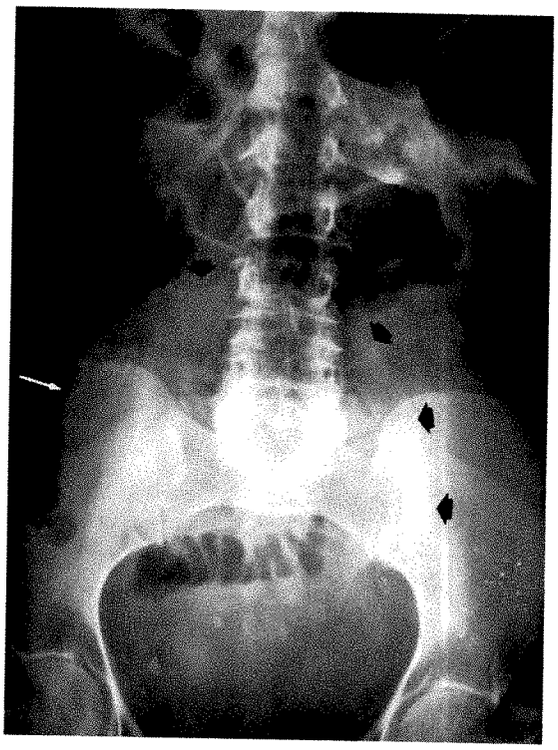


FIG. 2. Supine abdominal roentgenogram of a 56 year old Negro housekeeper with a 24 hour history of severe aching epigastric pain, vomiting, chills and sweating. Pelvic examination suggested a mass filling the pelvis. A diagnosis of twisted or ruptured ovarian cyst was made, but exploratory laparotomy showed almost the entire small bowel to be infarcted. The upper margin of the pseudotumor produced by the edematous fluid-filled loops of small bowel is well seen (arrows).

endothelium of the capillaries result in blood soaked, deep blue bowel wall throughout the involved area. The end result of venous obstruction is similar, although the changes are congestive from the onset and occur at a slower rate than those following arterial obstruction.[11]

The roentgenologic signs which may lead one to suspect intestinal infarction on the basis of plain roentgenograms are those of paralytic ileus, the accumulation of fluid in the lumen, or the thickening of the bowel wall of the infarcted segment. Localized or generalized distention of the intestine usually simulates a mechanical obstruction, which may have a distribution corresponding to that of the superior mesenteric artery and vein with an abrupt demarcation of the distended intestine near the hepatic or splenic flexure of the colon (Fig. 1).[5] This "characteristic" distention is comparatively rare, however, and probably occurs only when the superior mesenteric artery or vein, rather than segmental branches, are occluded. Another interesting finding occurs when fluid-filled small bowel loops create a soft tissue mass, the so-called "pseudotumor" (Fig. 2) described by Frimann-Dahl.[5]

Sometimes there are seen rigid, thick-walled, fixed loops containing minimal collections of luminal gas which remain unchanged in distribution on upright or decubitus roentgenograms. This finding is due to edema of the wall of the small intestine and is highly suggestive of mesenteric venous obstruction[17] (Fig. 3). Intramural gas and gas in the portal venous system are usually signs of advanced disease and, although diagnostic of intestinal

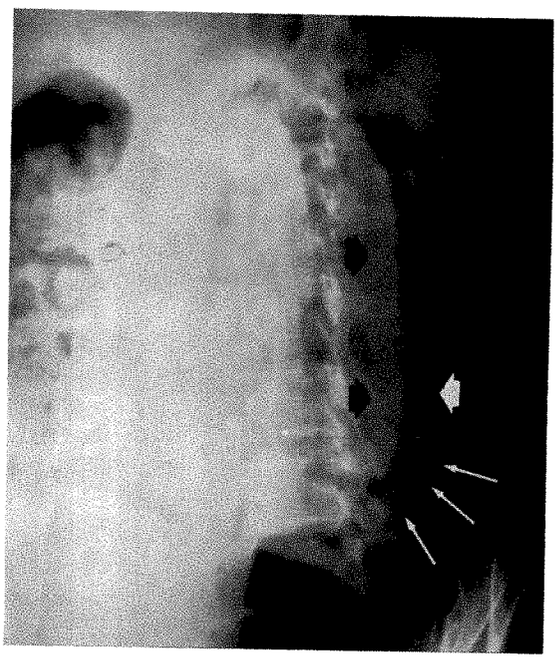


FIG. 3. Right lateral decubitus roentgenogram of a 49 year old female showing a long, rigid thick-walled loop of bowel on the left side of the abdomen without detectable fluid levels. Autopsy demonstrated portal and mesenteric vein thrombosis and infarction of the jejunum. The edges of the thickened jejunal loop are indicated by the arrows.

necrosis, are unfortunately seen late in the course of the disease.[18,19]

Although the findings previously discussed are helpful in making the diagnosis of infarction of the bowel when present, it should be noted that many patients with extensive intestinal infarction and obvious clinical signs of a major abdominal catastrophe will have no detectable roentgenologic abnormality.

ROENTGENOLOGIC MANIFESTATIONS OF VASCULAR AND HEMATOLOGIC DISORDERS AS SHOWN ON ROUTINE BARIUM STUDIES OF THE SMALL INTESTINE AND COLON

The roentgenographic findings due to chronic ischemia of large segments of the intestine caused by obstructive lesions of the proximal portions of the celiac, superior mesenteric, and/or inferior mesenteric arteries are frequently nonspecific.



FIG. 4. Barium enema study of a 54 year old white female with a 3 year history of "colitis." She had had intermittent crampy abdominal pain and diarrhea, which had become worse during the last year and severe during the last 3 months. Roentgenographic changes in a short segment of proximal transverse colon (arrows) suggest inflammatory disease. The acute abdominal pain resulted in exploratory celiotomy which showed early infarction of the small bowel and colon. She became asymptomatic after endarterectomy and her previous symptoms and mucosal changes in the colon were attributed to chronic intestinal ischemia.



FIG. 5. Small bowel examination of the patient presented in Figure 4. This examination was done just before the celiotomy which demonstrated extensive early infarction of the small bowel and colon. Not only are the jejunal loops edematous and spastic, but marginal scattered "thumbprints" (arrows) are seen. The changes are those of an acute infarction as opposed to the colon changes (see Fig. 4) which had been demonstrated on several examinations during the 3 previous years.

The appearance of the small bowel may suggest sprue because of the "disordered motor function" or "malabsorption" patterns. In fact, there is often accompanying clinical evidence of malabsorption due to the impaired physiology of the small intestine.[9,16] Furthermore, the roentgenologic manifestations of nonspecific thickening of the mucosa and the ulcers in the small or large bowel (Fig. 4) often resemble inflammatory conditions such as regional enteritis, granulomatous colitis, or ulcerative colitis, although they are the result of advanced chronic vascular disease.[2,11,20,21,24] It is possible that intestinal flora invades the involved mucosa and contributes to these changes.[23]

The roentgenographic changes due to extensive infarction or acute segmental infarction following embolization or thrombosis are frequently more specific than the aforementioned chronic changes, and are manifestations of severe mucosal edema and localized or diffuse intramural hemato-

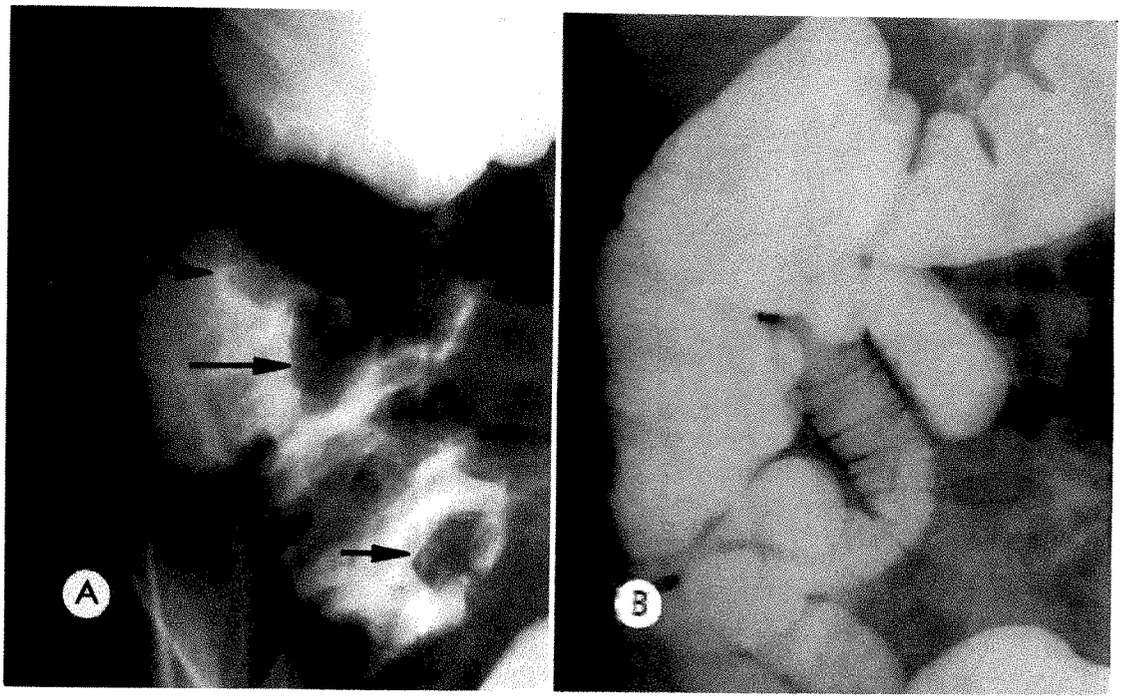


FIG. 6. (*A*) Barium enema study showing segmental infarction of the cecum and ascending colon in a 45 year old man, 25 days after myocardial infarction. The involved area was spastic and shows transverse ridging plus large localized hematomas (arrows). Selective superior mesenteric arteriogram showed embolic occlusion of the ileocolic artery. (*B*) Repeat barium enema study 7 weeks later shows complete healing except for slight contracture of the cecum.

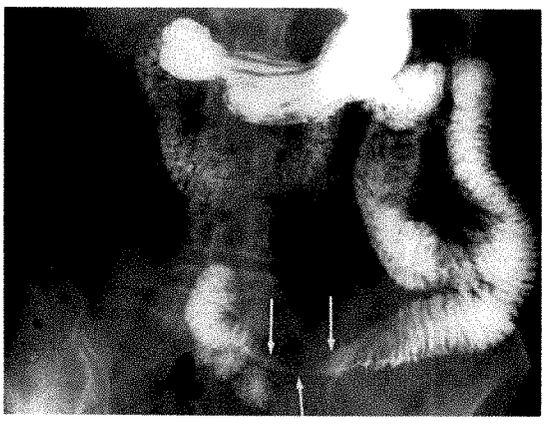


FIG. 7. Gastroduodenal and small bowel roentgenograms of a 70 year old white female showing a 6 cm. smooth benign appearing stenotic area (arrows) in the upper jejunum with slight dilatation of the jejunal segments proximal to the lesion. At the time the lesion was first identified, the patient stated that she had an acute episode of severe abdominal pain 3 months earlier, followed by repeated postprandial vomiting. Her vomiting subsided gradually and she refused surgery. During 20 months of observation, she has remained well and the upper jejunal lesion has remained unchanged. However, the jejunum proximal to the lesion is becoming more dilated, suggesting that the lesion is becoming more stenotic. No history of ingestion of thyazide diuretics or potassium therapy could be elicited. Although this is not a proven case, the history and subsequent clinical and roentgenographic course are classic for an acute segmental jejunal infarction followed by segmental fibrosis and partial upper jejunal obstruction.

mas. The "thumbprints"[20] due to localized hematomas, the transverse ridging[20,21] and the "stack of coins"[10,22] appearance caused by more diffuse dissections of blood are characteristic of such intramural hemorrhage. Thus, although one does not often have the opportunity to examine the small bowel with barium sulfate during the early acute phase of an infarction resulting from sudden obstruction of the superior mesenteric artery, the edematous, slightly dilated, churning loops with scattered marginal "thumbprints" and moderate intralumi-

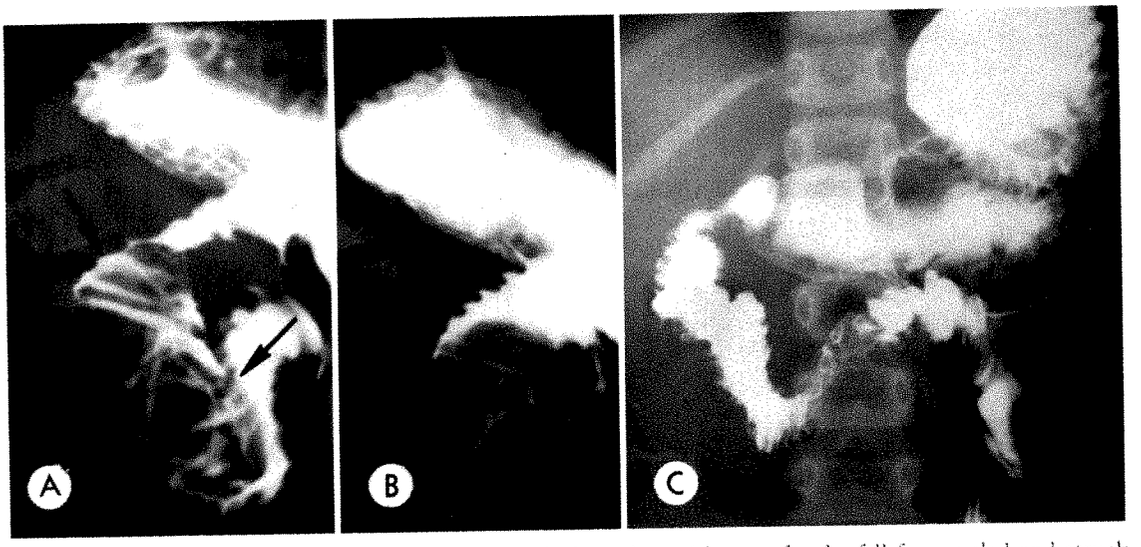


FIG. 8. Gastroduodenal examinations of a 12 year old boy about 6 hours after he fell from a sled and struck his abdomen on a tree stump. (*A*) There is seen an obstruction in the second part of the duodenum with submucosal masses (arrows). (*B*) There is also a slight "coil spring" appearance on the later films. These changes were considered typical for a submucosal hematoma. Recovery was uneventful without surgical intervention and (*C*) repeat gastrointestinal examination 9 days later showed only slight residual thickening along the involved segment.

nal fluid (Fig. 5) are easy to correlate with the pathologic process present.

Areas of acute segmental infarction (Fig. 6*A*) with "thumbprints," transverse ridging and spasm have an even more characteristic roentgenographic appearance and usually allow a correct diagnosis to be made. If the infarcted segment involves, or is localized to the small bowel, the "stack of coins"[10] appearance may be present due to the diffuse intramural dissections of blood. Some of these areas of infarction may return to normal (Fig. 6*B*) due to the development of collateral vascularization or recannulization of the obstructed artery. Less adequate revascularization sometimes leads to the development of a fibrotic benign stricture (Fig. 7) of the affected segment of bowel. In view of the stenotic lesions which sometimes follow segmental infarctions, it is interesting to note that Louw and Barnard[14] were able to produce typical intestinal atresias in puppies by intrauterine ligation of segmental mesenteric vessels. However, if the infarction is extensive, there will be necrosis of the entire bowel wall with perforation and an abdominal catastrophe.[20,25] Intramural hematomas secondary to trauma (Fig. 8, *A*, *B* and *C*) may produce a picture similar to an area of acute infarction,[4,13] usually in the duodenum.

The roentgenographic changes seen on barium sulfate examinations of the small bowel and colon in patients with intramural intestinal hemorrhage due to hematologic disorders, such as hemophilia, thrombocytopenic purpura and anticoagulant therapy, are similar to those seen following infarction due to vascular occlusions. However, the involved segment of bowel in purpuric disease is usually quiet and placid in sharp contrast to the irritable, often spastic, segment seen following infarction.

The diffuse small artery and capillary disease associated with periarteritis nodosa (Fig. 9, *A* and *B*) and Henoch-Schönlein's purpura (Fig. 10*A*) may produce widespread roentgenographic changes which appear to be inflammatory in nature,[1,6] and which thus must be differentiated from acute ulcerative colitis or ileocolitis. Careful evaluation of the contrast

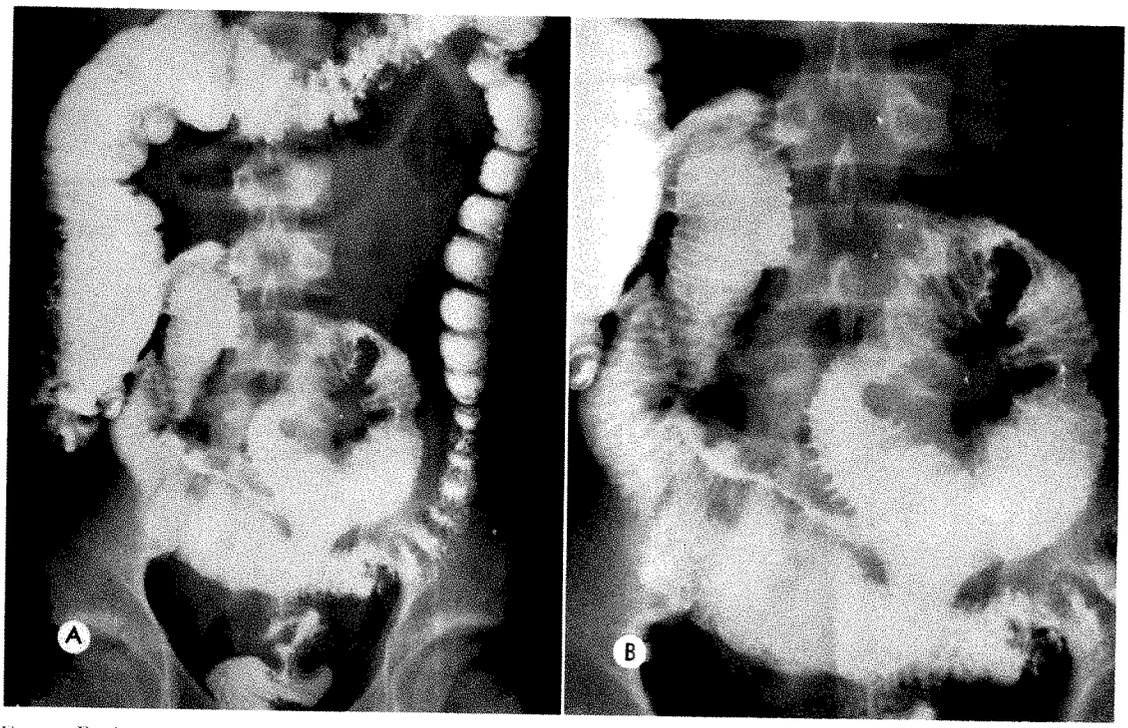


FIG. 9. Barium enema studies of a 16 year old white male who presented with a 1 week history of persistent, dull crampy abdominal pain with nausea and vomiting. (*A*) Bloody diarrhea had occurred during the 24 hours preceding this examination. (*B*) The multiple mucosal or submucosal nodules throughout the colon and transverse ridging plus dilatation of the ileum were felt to represent the changes of acute ileocolitis. In retrospect, the ileal loops show the "stack of coins" appearance of extensive intramural hemorrhage. At operation, the entire small bowel was reddish and granular with a thick hyperemic wall. Three areas of necrosis with perforation were found. The colon was hyperemic with mucosal edema. A diagnosis of acute periarteritis nodosa was made by the pathologist and the patient died with progressive central nervous system and renal involvement 3 weeks later.

studies of the small bowel and colon will frequently (Fig. 10*B*) show enough evidence of "thumbprints" and the "stack of coins" appearance to indicate a more specific diagnosis of intramural hemorrhage.

DISCUSSION

Diagnostic difficulties occur because chronic ischemic and inflammatory diseases of the small intestine and colon can cause similar roentgenographic appearances. Thus, patients with roentgenologic findings suggesting inflammatory disease of the intestine, particularly if they have generalized arteriosclerosis and/or abdominal bruits, should be considered for angiographic studies. However, most children or young adults with typical clinical and roentgenographic evidence of an inflammatory small bowel or colon disease can be spared such investigation.

Fortunately, the roentgenographic changes due to intramural hemorrhage and acute segmental infarction are more specific than those due to chronic ischemia, and usually result in a more accurate and diagnostic interpretation. Identification of the possible etiology of the changes seen (*e.g.*, a recent myocardial infarction as the likely source of an embolus) will help differentiate localized intramural hemorrhage from acute segmental infarction.

In spite of the fairly characteristic roentgenographic changes of intramural hemorrhage, they are not absolutely diagnostic. It should be remembered that submucosal thickening from other causes such as neoplastic infiltrate, amyloid deposits or edema

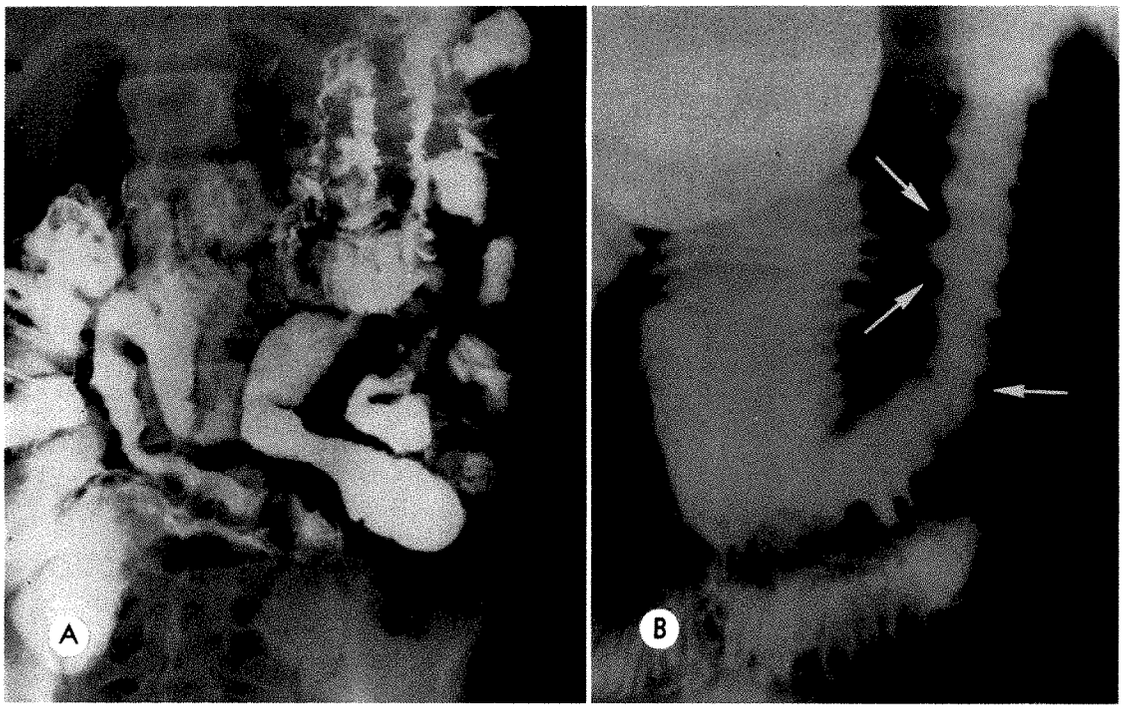


Fig. 10. Small bowel examinations of a 19 year old white male who presented with petechiae and purpuric spots over both lower extremities and a history of mild migratory joint pain and crampy abdominal pain and vomiting during the previous week. A diagnosis of Henoch-Schönlein's purpura was made. (*A*) The generalized mucosal thickening, with prominent folds and areas of both luminal dilatation and narrowing plus excessive intraluminal fluid superficially, resembles extensive regional enteritis but (*B*) careful evaluation shows transverse ridging and multiple "thumbprints" (arrows) consistent with intramural hemorrhage. The patient gradually improved during extensive steroid medication and the roentgenographic appearance of the small bowel returned to normal after several weeks.

fluid due to hypoproteinemia, etc., can produce similar roentgenographic findings. Figure 11 is a representative roentgenogram of the barium filled small bowel of a 42 year old woman with chronic lymphatic leukemia. The striking "stack of coins" appearance and transverse ridging remained unchanged for several years in the absence of any acute clinical symptoms. The possibility of submucosal hemorrhage or generalized infarction was, therefore, felt to be small. She maintained normal prothrombin and platelet levels throughout this period, but the serum proteins were consistently low. The small bowel changes are believed due to submucosal edema or leukemic infiltrate.

There have been several interesting observations concerning the possible role of vascular disease in obscure intestinal disorders. Necrotizing colitis proximal to obstructing neoplasms of the colon and regional enteritis appearing after abdominal trauma have been reported[7,8] and the basic abnormality in these conditions may be interference with blood flow.

Patients with both ulcerative colitis and portal hypertension have been reported to show improvement of their colon after portocaval shunt.[15] It may be that increased blood flow due to the lowered venous pressure is beneficial to the diseased mucosa.

SUMMARY

Representative cases of vascular and hematologic disease affecting the small bowel and colon have been discussed with emphasis on the information which can be derived from the plain roentgenograms and

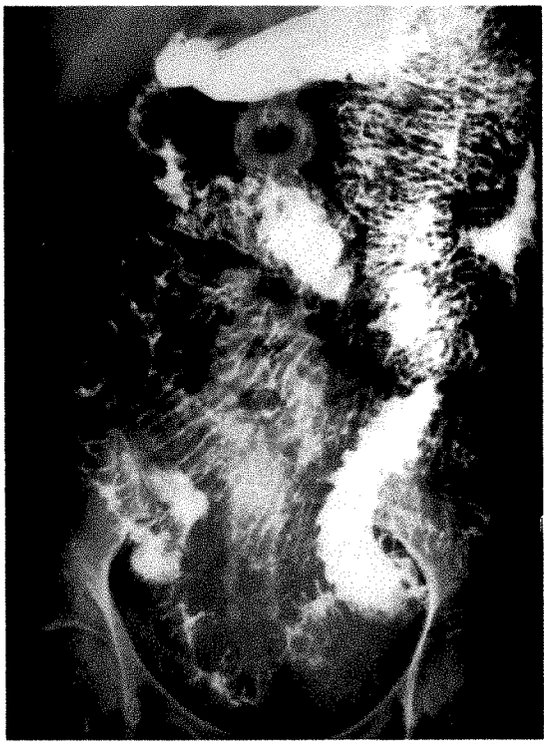


FIG. 11. Small bowel roentgenogram of a 42 year old woman with chronic lymphatic leukemia. The transverse ridging and "stack of coins" appearance suggest extensive submucosal hemorrhage. However, at no time during the several years she was followed did she have any bleeding difficulty or acute clinical symptoms. The roentgenographic appearance of the small bowel was unchanged for several years. She did have persistently low serum protein levels and these roentgenographic changes are attributed to submucosal edema or chronic leukemic infiltrate.

routine roentgenologic contrast studies of the small bowel and colon. Careful analysis of these initial studies will frequently allow not only an accurate diagnosis, but a proper selection of patients for the more complex angiographic or surgical studies.

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IATROGENIC JEJUNAL ULCER

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UNTIL recently, nonspecific ulceration of the small intestine has rarely been reported. A majority of such cases has been considered idiopathic in nature.[9] Causal factors proposed as credible in some individual cases include the Zollinger-Ellison syndrome, an obscure vascular disorder[8] or an atypical regional enteritis.

A striking increase in the clinical incidence of primary jejuno-ileal ulcers is now attributed to an iatrogenic mechanism: oral potassium administration.[1,2,4,5,6]

Characteristic roentgen features have been observed in patients with a small bowel "ulcer-stenosis-dilatation complex." Such findings are well illustrated in the following case report of a hypertensive patient whose treatment shortly preceded the discovery of this probable causative mechanism. Since the diagnosis is wholly dependent upon roentgen examination, description of the single case appears warranted in order to emphasize the manifestations of the syndrome to radiologists.

REPORT OF A CASE

The patient, a 41 year old obese male, was initially hospitalized on August 9, 1960 for investigation of hypertensive cardiovascular disease first detected during an office examination. Upon admission, the blood pressure was 212/136. Laboratory and roentgenographic studies, including excretory pyelography, were negative.

Response to chlorothiazide (diuril, 500 mg. twice daily) was satisfactory and the patient was dismissed on August 19, 1960. During the 10 day period of hospitalization, the patient lost 20 pounds in weight. Blood pressure readings at the time of discharge averaged 130/80.

A second period of hospitalization was necessitated by the onset of a sciatic compression syndrome exactly 4 years later. On August 9, 1964, the date of the second admission, the patient was normotensive as he had remained since the inception of thiazide medication. Hydrochlorothiazide with enteric-coated potassium chloride (hydrodiuril Ka, 50 mg. daily) was now prescribed. Roentgenographic spinal examination revealed narrowing of the lumbosacral disk space. The patient responded to treatment by hot packs, massage and ultrasound and stated that he was asymptomatic on discharge on the 11th hospital day, August 20, 1964. Nevertheless, on August 26, 1964 the patient was readmitted because of cramping abdominal pain, nausea and vomiting. He now admitted to a long-standing aversion to fried and fatty food and to having experienced much bloating, belching and flatus during his recent hospitalization. He had not reported these symptoms because he did not regard them as significant. These had increased in frequency and severity during the 6 days since discharge.

Inasmuch as admission blood pressure determinations were normal, the thiazide regimen was discontinued. (In summary, the patient had received diuril daily for 4 years and hydrodiuril Ka for 17 days prior to the third hospital admission.)

Physical examination indicated only mid-epigastric tenderness to deep palpation. Survey abdominal roentgenograms showed several partially calcified gallstones and distended jejunal segments suggestive of an early sentinel paralytic ileus. Consecutive cholecystograms on the following 2 days demonstrated a nonfunctioning gallbladder.

A barium meal study was next performed principally for the sake of completeness prior to cholecystectomy. The gastroduodenal segments were unremarkable, but the proximal jejunum was generally dilated. Serial projections revealed a focal constriction of the distal jejunal loop situated in the right inferior abdomen. This was initially outlined by air and subsequently opacified by barium (Fig. 1). The stenotic lesion was 15 mm. in length, concentric and merged abruptly with adjacent distended bowel with normal connivent valves. There was no roentgen evidence of ulceration or tumefaction.

Following cholecystectomy and incidental

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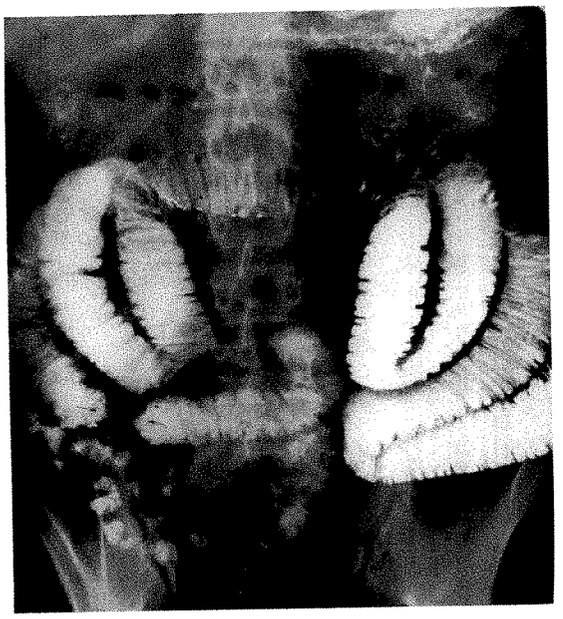


Fig. 1. Small intestinal projection demonstrating faceted gallstones at upper arrow. Jejunal dilatation is proximal to a focal bowel constriction (lower arrows).

appendectomy, the jejunal constriction was readily identified and a 100 mm. segment was resected for what the surgeon assumed to be a focal regional enteritis. At this site of narrowing, the bowel was thickened and inflamed. Proximally, the jejunum was dilated but was otherwise negative.

The pathologic report disclosed that the gallbladder specimen showed a subacute and chronic cholecystitis with cholelithiasis. The appendix was free of abnormality. The small intestinal segment contained a constricted area approximately 15 mm. in length in which portion, the bowel wall was slightly thickened and hemorrhagic. On the mucosal aspect, there was a shallow ulcer which measured approximately 15×5 mm. and had a green shell-like structure along its base. Multiple jejunal sections showed a relatively normal jejunal mucosa gradually merging with an ulcerated area. Here, a fibrous connective tissue base was diffusely infiltrated with polymorphonuclear neutrophils, eosinophils, lymphocytes and plasma cells. In a very occasional area there was a small amount of granulation tissue and a fibrin covering. The ulceration extended below the muscularis mucosae. The underlying submucosa was thickened with mature fibrous connective tissue and also infiltrated with inflammatory cells. The muscular coat and the serosa showed a similar inflammatory infiltration. In the central area of the ulcer, there was an increased number of lymphatic vessels as compared with the surrounding submucosal tissue.

The pathologist concluded that the ulcer of the jejunum showed many of the features which had been associated with enteric-coated potassium and thiazide therapy. Gross examination showed a shell-like structure present in the ulcer, suggesting the possibility of remnants of one of these tablets. This, of course, disappeared from the microscopic specimen during processing.

The postoperative course was uneventful. Barium studies were repeated 9 weeks following operation. No digestive tract abnormality could be demonstrated on this occasion.

DISCUSSION

Rapidly accumulating evidence links enteric potassium as a causal factor to a unique superficial ulcer of either the distal jejunum or ileum. Roentgenologically, an ulcer niche is seldom identified. The demonstrable intestinal stenosis is a circumferential, short and abruptly marginated solitary lesion. Submucosal fibrosis beneath the ulceration causes thickening of the bowel wall with contraction. Proximal intestinal dilatation is accompanied by clinical signs of partial obstruction.

Boley *et al.*[4] have cited experimental data to support clinical impressions that enteric-coated potassium chloride is the responsible agent in the formation of drug-induced small bowel ulcers. "The release and absorption over a short segment of intestine which enteric coating may permit is the direct cause of these lesions. It is our belief that a high concentration of potassium chloride in the veins of the absorbing segment of intestine results in venous spasm or paralysis, venous stasis, submucosal edema, and subsequent ulceration."

This theory of a vasculogenic mechanism has supplanted the natural conclusion that an orally administered agent ulcerates the intestine by a topical, escharotic action.[1,6]

Complete and rapid clinical recovery

may follow mild degrees of injury. With more severe degrees of damage, fibrosis with increasing stenosis produces progressive intestinal obstruction. The most severe injuries produce perforation or intraluminal hemorrhage.[3]

SUMMARY

A case of jejunal ulceration in a hypertensive male on a thiazide-potassium regimen is reported. Roentgenologically, the process was manifest by focal constriction with proximal dilatation.

Small intestinal ulceration should be considered in the differential roentgen diagnosis of obscure jejuno-ileal stenosis or obstruction, particularly in patients receiving enteric-coated potassium medication.

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VOL. 99, NO. 1

MECKEL'S STONE ILEUS*

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BRYN MAWR, PENNSYLVANIA

A LAMINATED calcification in the right lower quadrant associated with an acute abdominal condition is very suggestive of the diagnosis of acute appendicitis.[2] With the added roentgen signs of small bowel obstruction, the diagnosis of gallstone ileus is also suggested. This report concerns another, and rarer, consideration which might be called "Meckel's stone ileus," a small bowel obstruction due to a large stone formed within a Meckel's diverticulum and arrested within the distal ileum.

Three previous reports of enteroliths formed within Meckel's diverticula causing intestinal obstruction can be found in the literature.[3,6,7] Preoperative roentgenograms were available in 2 of these cases, but in neither case was there sufficient density of the enterolith to record a shadow on the roentgenogram. In none of these cases, as well as in this report, was the correct diagnosis considered preoperatively.

That calculi occur within Meckel's diverticula is well documented. Boldero[5] reports 1 case and reviews 16 others. In only 2 of these cases were the calculi demonstrated prior to surgery. Bischoff and Stampfli[4] suggest a characteristic folded ribbon-like calcification which might suggest stone formation within a Meckel's diverticulum. However, in a large series, Weinstein *et al.*[10] did not mention calculi or enteroliths in the 162 cases in which surgery was prompted by acute conditions involving Meckel's diverticula. In addition to 15 cases with intussusception, 28 of their patients had intestinal obstruction.

REPORT OF A CASE

A 48 year old female was admitted to the Bryn Mawr Hospital on December 9, 1965 with a 2 week history of intermittent abdominal pain

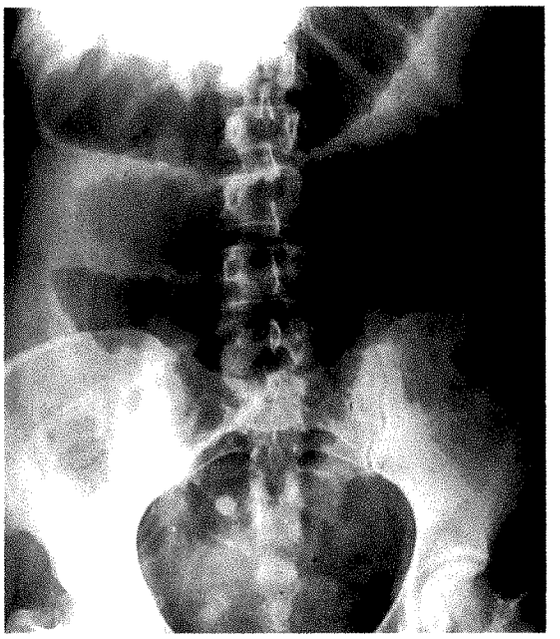


FIG. 1. Anteroposterior roentgenogram of the abdomen showing right lower quadrant calcification and marked distention of the small bowel without colon gas.

associated with increasing nausea and vomiting. She denied hematemesis, and the vomitus had become brown with a fecal odor within the last several days. Her last bowel movement was 2 days prior to admission and this was produced with an enema. She had had an appendectomy 11 years previously.

Physical examination revealed an acutely ill somewhat obese white female. Her temperature on admission was 100° F., blood pressure 110/70, and pulse 100 and regular. On abdominal examination there was generalized distention, but no palpable masses. Tenderness was elicited throughout the abdomen, and peristalsis was hyperactive. A healed right lower quadrant incision was present. Rectal examination was negative. A Levin tube was placed in the stomach and approximately 1,500 cc. of a brown, foul smelling liquid was aspirated.

The hemoglobin was 14.7 gm., and a white blood cell count of 7,725 was obtained with 85

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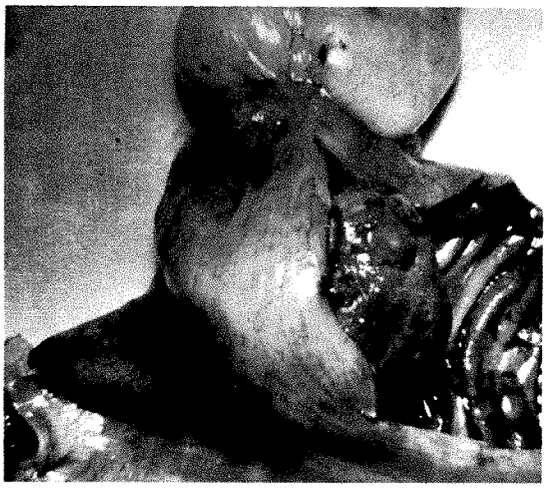


FIG. 2. Operative specimen opened to show enterolith *in situ*.

per cent neutrophiles, 13 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was negative except for a proteinuria of 25 mg. per cent.

Roentgen examination of the abdomen (Fig. 1) revealed multiple distended loops of small bowel without evidence of colon gas. In addition, there was a laminated opacity measuring 12 mm. in diameter in the right lower quadrant. The character of the calcification suggested a gallstone, and not a mesenteric lymph node. On the decubitus roentgenogram there were multiple varying air fluid levels noted within the small bowel, and no change in the position of the laminated calcification. With the history of previous appendectomy, and despite the absence of air within the biliary tree, a preoperative roentgen diagnosis of small bowel obstruction with possible gallstone ileus was made.

At laparotomy, performed 3 hours after admission, an inflammatory mass was found in the right lower quadrant which represented a large Meckel's diverticulum. An adhesion had formed from the tip of the diverticulum to the right lateral pelvic wall, and behind this, a loop of bowel had slipped, producing a partial obstruction. In addition, there was a fecal ball, measuring 35 mm. in diameter which lay free within the small bowel. This appeared to have dropped out of the Meckel's diverticulum and was prevented from passing distally by the partial obstruction secondary to the adhesion (Fig. 2). The adhesion was divided and the small bowel including the Meckel's diverticulum and the enterolith was transected and a primary small bowel anastomosis was performed. The patient's postoperative course was uncomplicated.

Histologic examination of the Meckel's diverticulum revealed a superficial ulceration within it, but no evidence of ectopic mucosa. Unfortunately, the presumed simple enterolith was discarded and no analysis of the central calcific core was made. Since it has been suggested that these calcifications may represent gallstones arrested within diverticula,[5] postoperative cholecystography was performed which was entirely normal.



FIG. 3. Roentgenogram of operative specimen showing central laminated core of enterolith.

SUMMARY

A case of intestinal obstruction is reported due to an enterolith formed within a Meckel's diverticulum associated with an adhesion and a trapped loop. Forming a cast of the lumen of the diverticulum, the enterolith, measuring 35 mm. in diameter (Fig. 3) was discharged into the ileum, precipitating the obstruction. Only the 12 mm. central core of the enterolith was visible on the preoperative roentgenogram.

This is the fourth reported case of this unusual form of intestinal obstruction and the name "Meckel's stone ileus" is proposed to describe the syndrome.

A laminated calcification in the right lower quadrant in the presence of small bowel obstruction should suggest this additional diagnostic consideration.

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PRIMARY CARCINOMA OF THE LIVER (HEPATOMA)

ITS DIAGNOSIS BY SELECTIVE CELIAC ARTERIOGRAPHY

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TAIPEI, TAIWAN

THE incidence of hepatoma varies geographically.[16] It is common among Chinese, and in Taiwan it is the most common neoplasm in males, accounting for 15 per cent of all neoplasms in that sex.[30] In the United States, on the other hand, it is a rarer disease,[24] although the incidence has been increasing recently, presumably as hepatitis increases in the Occident.[4,19] With improvement in anesthesia and surgical techniques, partial hepatectomy has become feasible and it offers the only hope for cure. Long-time survival following such surgery has been reported.[12] Accurate preoperative, angiographic delineation of the extent and location of the tumor is of the greatest importance to the surgeon. Bierman *et al.*[7] described the arteriographic findings 14 years ago, but there have been only a few subsequent publications.[8,25,28]

In the Department of Radiology of the Veterans General Hospital in Taiwan, we have used selective celiac arteriography in cases of primary hepatoma for a period of a little less than 2 years and a summary of our findings in 50 cases seen during that period is presented.

TECHNIQUE

A catheter is introduced through the femoral artery using the Ödman technique.[23] After heavy sedation, the patient is placed supine on the roentgenographic table and the skin over the inguinal area is prepared in the usual manner. Following local anesthesia, a Seldinger[26] arterial needle is inserted into the femoral artery at a point about 2 cm. below the inguinal ligament, usually on the right side. Under fluoroscopic control, a flexible metal spring guide wire is inserted through the needle and advanced gently into the lower part of the abdominal aorta. The arterial needle now is removed and a flexible, yellow Ödman-Ledin radiopaque catheter with a premolded tip is threaded into and along the artery. After removal of the guide wire, the catheter promptly resumes its premolded shape and, as it is turned anteriorly and manipulated under fluoroscopic control, the tip can be maneuvered into the opening of the celiac axis (usually situated between the 12th thoracic and 1st lumbar vertebral bodies). If there is a question as to the location of the catheter tip, a small amount of contrast material sometimes is injected. As soon as satisfactory placement has been accomplished, the table top is shifted until the patient's abdomen is centered over a rapid-film changer. The contrast medium now is injected (30–40 ml. 50 per cent hypaque*), either manually or mechanically, the entire injection being completed in from 3 to 4 seconds. Beginning with the start of injection and continuing at the rate of 1½ films per second a series of approximately 15 films is exposed. Usually, patients experience no pain and following removal of the catheter, continuous pressure applied to the arterial puncture site for a period of from 10–20 minutes suffices to prevent hemorrhage.

Between May, 1964 and October, 1965, we conducted examinations of this sort on 82 patients, who had various types of liver disease. Fifty of the lesions proved to be primary hepatoma (hepatocellular carcinoma); there were no cholangiomas (bile duct carcinoma). In 32 of the 50, confirmation was obtained by means of percutaneous liver needle biopsy, in 12 by surgical exploration, and in 6 by autopsy. Forty-nine

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of the 50 cases were males; the oldest was 67 years old, the youngest 32, and the median age was 52 years. In 1 case, anomalies of the celiac artery made it impossible to get the catheter tip into that artery and it was necessary to be satisfied with injection into the abdominal aorta close to the origin of the celiac artery. In none of the cases have there been complications of any sort.

ILLUSTRATIVE CASES

Case 1. L. H. W. #7431, a 36 year old male, presented with general malaise, severe right upper abdominal pain and weight loss of 4 months' duration. The liver was enlarged to 7 cm. below the right costal margin.

Selective celiac arteriography: a dilated hepatic artery and a 10 cm. × 10 cm. solitary hypervascular tumor in the upper part of the right lobe of the liver, as well as displacement and stretching of neighboring hepatic arteries were demonstrated. The presence of contrast medium in the portal vein in the arterial phase was indicative of arteriovenous fistula (Fig. 1). A tumor stain was seen in a later phase (Fig. 2).

Arteriographic diagnosis: huge solitary hepatoma.

Needle biopsy showed necrotic cirrhosis with hepatocellular hepatoma.

At surgery, hepatoma located chiefly in the right lobe of the liver was found.

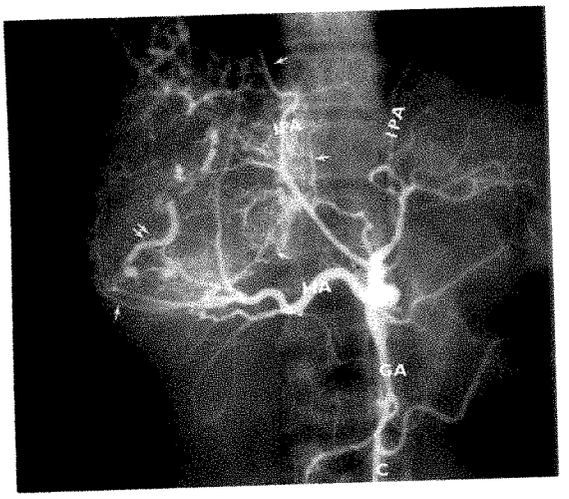


Fig. 1. Case 1. Solitary massive primary hepatoma. Selective celiac arteriogram made in arterial phase, 1½ seconds following onset of injection of 30 cc. 50 per cent hypaque. The catheter (C) lies with its tip in the celiac axis (CA). The hepatic artery (HA) is dilated. Large solitary hypervascular tumor in upper part of right lobe of liver. Tumor vessels within mass and adjacent arteries stretched and displaced (→). Arteriovenous shunt is indicated by opacification of portal vein (⇉) in this, the arterial phase. The gastroduodenal artery (GA) is displaced to the left. The two inferior phrenic arteries (IPA) rise from the celiac axis.

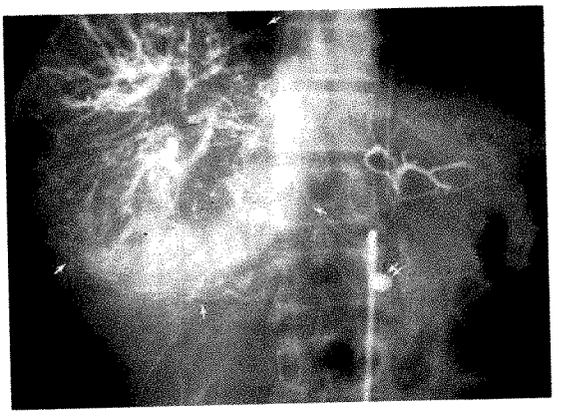


Fig. 2. Case 1. Seven seconds later (venous phase). Delayed clearing of contrast from tumor (→). There is probably a small aneurysm of the celiac axis (⇉), but it could not be identified at subsequent surgery.

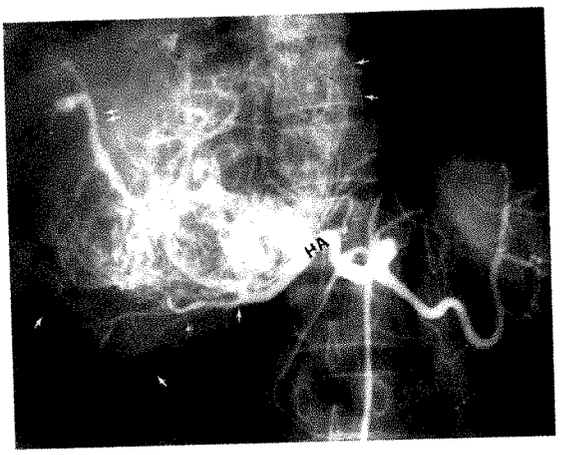


Fig. 3. Case II. Solitary massive primary hepatoma. Arteriogram made 2 seconds following onset of injection of 25 cc. 50 per cent hypaque through catheter in celiac axis. A 10 × 12 cm. hypervascular tumor in right lobe of liver. Adjacent vessels stretched and displaced (→). Early opacification of portal vein (⇉) indicative of arteriovenous shunt. Tumor nodules and vessels within tumor. Hepatic artery (HA) markedly dilated.



Fig. 4. Case II. Arteriogram made 8½ seconds following onset of injection. Delayed clearing of contrast medium from tumor (→) and from portal vein (⇒). Two additional small tumor nodules now show up (Z).

Case II. C. T. Y. #69013, a 37 year old male, presented with general malaise, anorexia and nausea of 4 months' duration and epigastric fulness and an enlarging mass for 1 month. The liver was palpable 4 cm. below the right costal margin and was firm and tender.

Selective celiac arteriography: large, solitary, highly vascularized tumor was seen in the right lobe of the liver. There were numerous tumor blood vessels and displacement of adjacent hepatic arteries. An arteriovenous fistula was evidenced by the early appearance of contrast medium in the portal vein in the arterial phase (Fig. 3). Pooling of contrast material in the tumor was noted in the late phase of the arteriogram (Fig. 4).

Arteriographic diagnosis: solitary hepatoma of right lobe.

The diagnosis was confirmed by subsequent percutaneous needle biopsy and laparotomy.

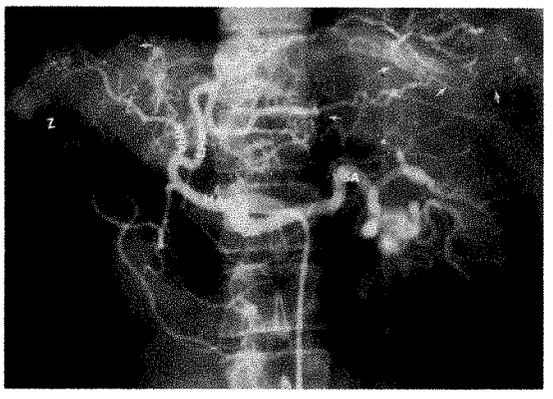


Fig. 5. Case III. Nodular type primary hepatoma. Arteriogram made 1½ seconds following onset of injection of 28 cc. 50 per cent hypaque. Dilatation of main hepatic artery (HA) and right hepatic artery (RHA). Left hepatic artery (LHA) particularly long, broad and tortuous and splenic artery (SA) abnormally tortuous. Both findings are indicative of cirrhosis. Right liver lobe is smaller than normal. Tumor vessels in both lobes (→). Calcified stone in gallbladder (Z).

Case III. H. T. J. #67307, a 51 year old male, presented with severe pain and epigastric fulness of 3 months' duration. A firm, nodular tender mass was noted 5 cm. below the xiphoid process.

Selective celiac arteriography: unusual dilatation, elongation and tortuosity of the left hepatic artery with tumor vessels in both lobes of the liver were demonstrated (Fig. 5). There were also numerous nodular shadows, from 1 to 3 cm. in diameter, and pooling of contrast material in the later phase of the arteriogram (Fig. 6).

Arteriographic diagnosis: cirrhosis of liver with a nodular form of hepatoma.

At laparotomy many firm nodules were found in both lobes of the liver.

Case IV. L. C. L. #67176, a 41 year old male, had had frequent attacks of loss of consciousness for a period of 2 months. The liver was palpable 7 cm. below the right costal margin. Severe hypoglycemia was found, the lowest fasting blood sugar level being 13 mg. per cent.

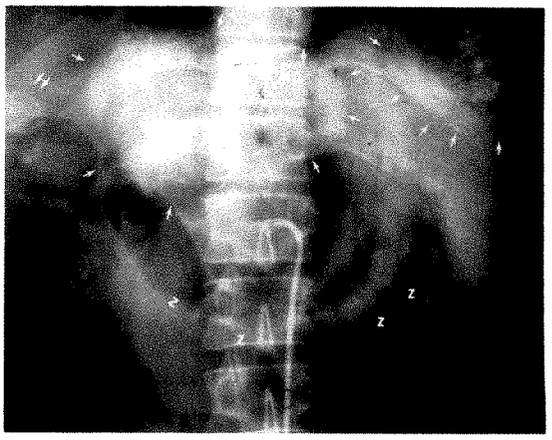


Fig. 6. Case III. Arteriogram made 8½ seconds following onset of injection. Pooling of contrast material in tumor nodules (→), opacification of gastric wall (Z), and opaque gallstone (⇒).

Alkaline phosphatase was 11.04 SJR units. The clinical diagnosis was either primary hepatoma or malignant insulinoma of pancreas with liver metastasis.

Simultaneous selective arteriography of celiac axis and of superior mesenteric artery: tumor vessels, particularly in the upper part of the right lobe of the liver, with stretching and distortion of intrahepatic arteries were demonstrated (Fig. 7). Numerous nodular tumor stains were noted in the later phase of the arteriograms (Fig. 8).

Arteriographic diagnosis: nodular form of primary hepatoma.

The diagnosis was confirmed by subsequent laparotomy and pathologic sections.

Case v. H. S. M. #16677, a 21 year old male, presented with epigastric pain and an enlarging mass over the right upper abdomen of 20 days' duration. The liver was tender and enlarged to about 5 cm. below the right costal margin.

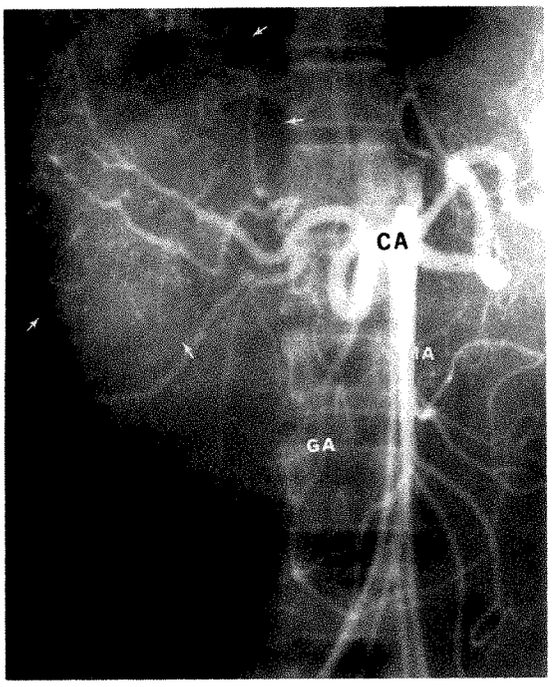


Fig. 7. Case iv. Nodular type primary hepatoma. Selective arteriogram 2 seconds following onset of simultaneous injection of 30 cc. 50 per cent hypaque into celiac axis (CA) and 20 cc. into superior mesenteric artery (SMA). Numerous tumor vessels in right lobe of liver. Intrahepatic arteries distorted (→). Gastroduodenal artery (GA) displaced slightly to the left.

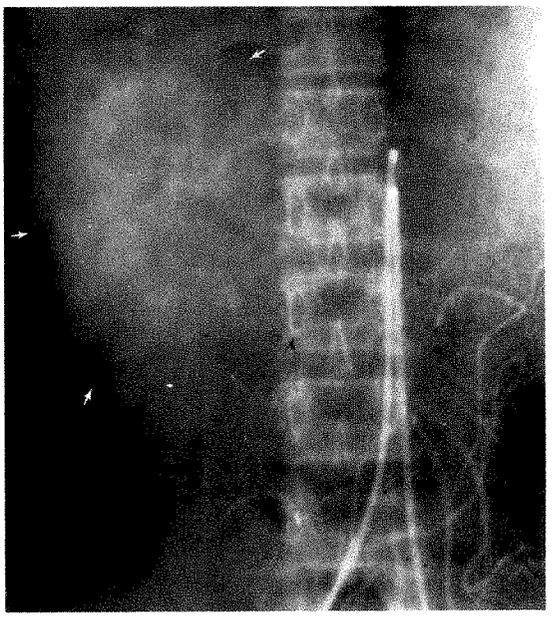


Fig. 8. Case iv. Arteriogram made 7½ seconds following onset of injection. Numerous tumor nodules in right lobe and presence of pooling or tumor stain (→).

Percutaneous selective celiac arteriography: dilated primary and branch hepatic arteries, with a short segment of narrowing of the proximal portion of the hepatic artery were seen. All

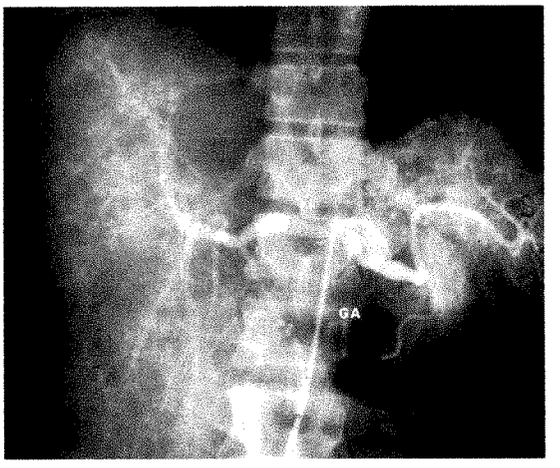


Fig. 9. Case v. Diffuse primary hepatoma. Arteriogram made 2 seconds following onset of injection of 30 cc. 50 per cent hypaque. Narrowing of short segment of proximal hepatic artery (HA) (⇉). Numerous tumor vessels through liver with stretching and distortion of all intrahepatic arteries. Gastroduodenal artery (GA) is displaced to left.

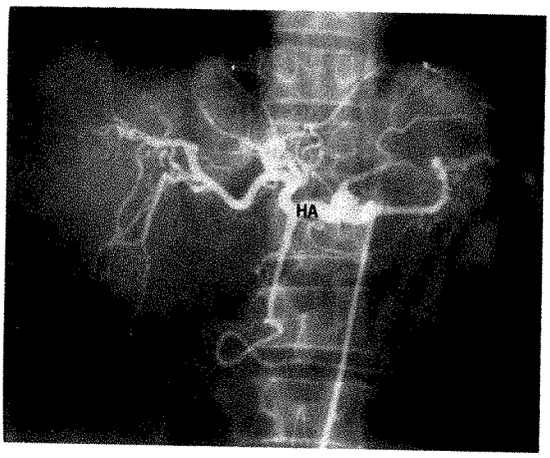


FIG. 10. Case VI. Another case of diffuse primary hepatoma. Arteriogram made 1 second following onset of injection of 25 cc. 50 per cent hypaque (0.25 mg. norepinephrine injected in advance of injection of contrast material). Hepatic artery (HA) dilated. Intrahepatic arteries distorted and tortuous.

intrahepatic arteries were markedly stretched and distorted. Tumor vessels were demonstrated throughout the liver (Fig. 9). A tumor stain was noted in the later phase of the arteriogram.

Arteriographic diagnosis: diffuse form of primary hepatoma.

The diagnosis was verified at subsequent laparotomy.

CASE VI. H. T. K. #69059, a 37 year old male, presented with general malaise, loss of weight and an enlarging mass in the right upper abdomen of 1 month's duration. The liver was enlarged, about 5 cm. below the right costal margin. The surface was nodular and tender.

Selective celiac arteriography: hepatic artery and branches were dilated with distortion and tortuosity of all the intrahepatic arteries (Fig. 10). Numerous tumor vessels were seen throughout the liver (Fig. 11). In the late phase of the arteriogram numerous tiny tumor nodules were demonstrated throughout the liver (Fig. 12).

Arteriographic diagnosis: diffuse form of primary hepatoma.

The diagnosis was verified by percutaneous liver needle biopsy.

In this case a small amount of norepinephrine had been injected through the catheter before the injection of the contrast medium in order to enhance filling of tumor vessels and the degree of the tumor stain.

DISTRIBUTION OF THE 50 CASES ACCORDING TO THE TYPE AND LOCATION

Three general types of hepatoma are recognized: They may be (1) massive, solitary tumors involving most or all of a lobe, usually the right; (2) nodular form with numerous nodules of varying size, located in one or more lobes; and (3) diffuse[5] (Table 1).

ANALYSIS OF ANGIOGRAPHIC FINDINGS

Dilatation of the hepatic artery. The hepatic artery was dilated in all 50 cases.

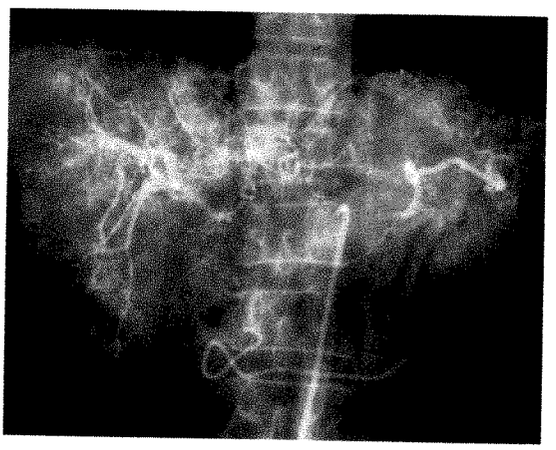


FIG. 11. CASE VI. Arteriogram made 4 seconds following onset of injection. Bizarre tumor vessels seen throughout liver.

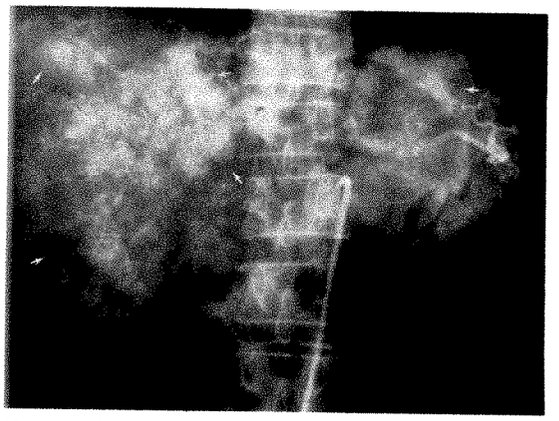


FIG. 12. Case VI. Arteriogram made 9 seconds following onset of injection. Throughout the liver, there are tiny tumor nodules in which contrast material has pooled, producing the so-called tumor stain (→).

Table I

DISTRIBUTION OF THE 50 CASES OF PRIMARY HEPATOMA ACCORDING TO TYPE AND LOCATION

Type	Location	No. of Cases	Per Cent
Solitary Massive	Right lobe	7	14
	Left lobe	1	2
Nodular	Right lobe	6	12
	Left lobe	3	6
	Both lobes	1	2
Diffuse		32	64
	Total	50	100

Dilatation probably results from increased functional demand by the neoplasm. If the primary hepatoma is of the solitary massive type, the branching intrahepatic artery supplying the tumor is relatively much wider than the others.

Displacement or stretching of the intrahepatic arteries. The solitary massive form of primary hepatoma displaces and stretches adjacent intrahepatic arteries (Cases I and II), and in the diffuse form distortion of the intrahepatic arteries is the rule.

Increased vascularity. Primay hepatoma is a highly vascular tumor[15] and angiography is practically the only means by which this characteristic can be demonstrated. Increased vascularity is most marked in the solitary massive and the nodular types (Cases I and II).

Tumor vessels. The presence of tumor vessels is a most important sign in the diagnosis of primary hepatoma and, without tumor vessels, such a diagnosis is of doubtful validity. Neoplasm is a strong stimulus to the formation of new blood vessels at the capillary level[2] and such newly-formed "tumor vessels," as defined by Strickland,[27] have a bizarre appearance. They are characterized by a purposeless arrangement, marginal irregularity, saccular dilatation and absence of orderly tapering as they extend peripherally. The identification of tumor vessels can be facilitated by the intra-arterial administration of small amount of norepinephrine prior to injection of contrast material.[1] Norepinephrine, a classical vasoconstrictor, reduces the caliber of normal arteries and arterioles as would be expected, but tumor vessels fail to constrict, apparently because of lack of normal neuromuscular and humoral response. As a result, an increased amount of opacified blood is shunted to them, facilitating their identification in arteriograms (Case VI).

Tumor stain or pooling of contrast material. Primary hepatoma, especially of the hepatic cell type, is richly vascularized and amorphous blood spaces occur within the tumor.[18] Contrast material remains in such spaces longer than in normal liver. Such delayed clearing of the contrast material is called pooling, or tumor stain. It is seen best in solitary massive or in nodular hepatomas (Cases I, II, III, and IV) and is one of the most important criteria for the diagnosis of primary hepatoma. As in the case of tumor vessels, pooling or tumor stain is potentiated by the intra-arterial administration of norepinephrine.

ARTERIOVENOUS SHUNT WITHIN THE TUMOR

Arteriovenous shunting is one of the characteristic pathologic findings of primary hepatoma.[15] Angiographically, it is evidenced by the early appearance of contrast material in the veins during the arterial phase. It is most marked in the solitary massive form (Cases I and II).

OTHER FINDINGS

Most primary hepatomas are associated with cirrhosis of the liver. Angiographically, cirrhosis is characterized by marked coiling and tortuosity of the intrahepatic arteries, the so-called "corkscrew" appearance (Case III). If the spleen is enlarged, the splenic artery usually is dilated and its course is more tortuous than normal (Case III). Cutoff of the gastroduodenal artery was noted

in 5 cases. Presumably, it is due to extrahepatic metastasis of the primary hepatoma. Displacement of the gastroduodenal artery to the left was seen in 19 cases, all having grossly enlarged livers. Segmental narrowing of the hepatic artery was seen in 3 cases. Apparently, this is due to invasion or compression by tumor.

DISCUSSION

There are no clinical features that are pathognomonic of primary hepatoma. History, physical examination and liver function tests are inconclusive in most cases.[21] Conventional roentgen examinations may yield some useful information. Elevation of the hemidiaphragm is a helpful sign, particularly if it is associated with evidence of esophageal varices,[25] or hematogenous lung metastasis.[31] Calcification of the liver has been reported chiefly in children.[20] Roentgenologic demonstration of displacement and extrinsic compression of adjacent organs, such as stomach, duodenum, colon and gallbladder,[13,31] is of some help, but is not specific. Thorotrast hepatolienography has been abandoned because it carries the hazard of inducing malignant disease.[29] Splenoportography is limited in usefulness because the splenoportogram of a liver enlarged by tumor may be identical to that seen in cyst or abscess.[14] The technical difficulty of performing hepatic venography and anatomic variation of the hepatic vein make that procedure impractical for clinical use.[10]

The liver has a triple vascular system, being supplied by the hepatic artery and the portal vein, and drained by the hepatic vein. It has been demonstrated repeatedly, however, that malignant tumors of the liver, whether primary or secondary, derive their blood supply exclusively from the hepatic artery.[6,11] Roentgen visualization of the hepatic artery, therefore, is a most valuable diagnostic method. Tumor vessels, tumor stain, arteriovenous shunts, dilatation of the hepatic artery and its branches, and displacement or stretching of the intrahepatic arteries provide a means of diagnosing not only the presence of hepatoma, but also its type and distribution. Angiography is helpful, therefore, in planning the clinical management of patients with primary hepatoma, whether they are to be treated surgically for a solitary lesion or by chemotherapy or irradiation for diffuse lesions.

LIVER SCANS

Scanning the liver following the administration of radioactive material is used in the diagnosis of the liver diseases, including primary hepatoma, but this procedure can demonstrate only large growths (at least 2 cm. in diameter), and occasionally fails to detect lesions of considerably greater size.[9,22] Furthermore, cysts and abscesses of the liver can scarcely be differentiated from a primary hepatoma by scanning.[3]

NEEDLE BIOPSY

Percutaneous needle biopsy of the liver is a helpful diagnostic procedure in primary hepatoma, but false negative specimens sometimes are obtained and the actual lesion is missed,[21] and sometimes, the amount of liver tissue obtained is inadequate[17] for pathologic study.

SUMMARY AND CONCLUSIONS

Selective celiac arteriography is a safe and important means of diagnosing primary hepatoma and, by establishing the type and distribution of the neoplasm, it facilitates the planning of therapeutic procedures. Angiography is indicated in epigastric masses of unknown nature; in patients suspected of having hepatoma; in patients whose livers are large and who are known to have primary neoplasms elsewhere in the body; and in those in whom needle biopsy has established the existence of primary hepatoma, but the type and distribution are unknown.

The arteriographic findings in 50 cases of proved primary hepatoma are described and discussed.

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CALCIFICATION IN PRIMARY LIVER CARCINOMA

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THE incidence of primary carcinoma of the liver in large autopsy series is about .6-.7 per cent.[6] The 2 main types of primary liver carcinoma are hepatic cell carcinoma and bile duct carcinoma. The hepatic cell carcinomas are about 3 times as frequent as bile duct carcinomas. Cirrhosis accompanies about 75 per cent of hepatic cell carcinomas and 30 per cent of bile duct carcinomas.

Calcification in metastatic disease of the liver has been reported by a number of authors.[1,3,4,8] The site of the primary lesion in the large majority of these cases has been the colon and most frequently the sigmoid colon. The calcification reported secondary to colon carcinomas is diffuse and finely granular. This has been likened to poppy seed calcification and appears to be typical for colon metastases. Other primary lesions with calcified liver metastases have been described. Cases of breast carcinoma[6] and melanoma[3] showed much larger and denser calcification than did the colon carcinomas.

Calcification in primary liver carcinomas is rare. Schroeder[7] and Karras *et al.*[3] have reported individual cases; both were bile duct carcinomas.

REPORT OF A CASE

A white male in 1955, at the age of 22 years, underwent surgery for bilateral varicose veins. In 1961, he was seen by his family physician for vague abdominal pains. At this time, it was noted that his varicose veins had recurred and that he had hepatomegaly. Surgery was performed for the recurrent varicosities in 1963. In June, 1964 he complained of bleeding hemorrhoids and a barium enema examination (Fig. 1) was done which showed extensive hepatic calcification. In January, 1965 because of shoulder pain and vague abdominal pains, gallbladder and upper gastrointestinal roentgenograms (Fig. 2, 3 and 4) were obtained and again showed the extensive liver calcification.

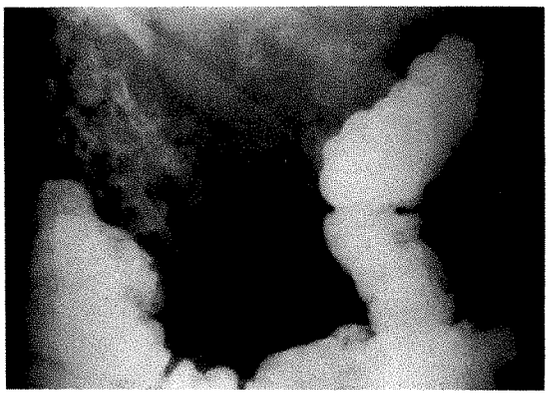


FIG. 1. Barium enema study on June 30, 1964. Extensive hepatic calcification which is not localized. The many spherical calcifications suggest calculi.

The patient was doing well until April, 1965 when he contracted varicella from one of his children and became jaundiced. He was admitted to the Cleveland Clinic and was explored on April 23, 1965. The right lobe of the liver was involved with multiple areas of dense infiltrative hard white scar tissue with calcifi-

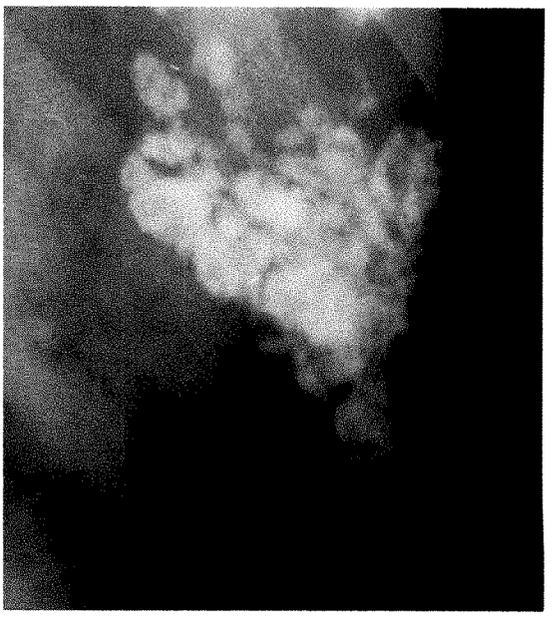


FIG. 2. Cholecystography on January 24, 1965 showed nonvisualization of the gallbladder.

cation, giving the appearance grossly of an infiltrative malignant hepatoma. The biopsy revealed fibrosis, calcification and biliary cirrhosis. He was discharged on prednisone. He was readmitted to the Cleveland Clinic in August, 1965 because of jaundice and rectal bleeding. It was decided that further surgery was inadvisable.

His condition deteriorated and he was admitted to Sharon General Hospital on October 21, 1965. He was markedly icteric and had massive ascites. Several days after admission he had hematemesis and became hypotensive. He expired on October 31, 1965 at the age of 32 years.

At autopsy, there was a large mass in the right lobe of the liver which was densely calcified. The gallbladder could not be found and appeared to be engulfed in the large calcific mass. There were areas in the mass which microscopically revealed a moderately differentiated bile duct carcinoma. Metastases were present throughout the omentum, lungs and pleura. There were large esophageal varices.

DISCUSSION

In the case reported by Karras *et al.*,[3] there were spherical calcifications which resembled calculi and inferior to this was an amorphous collection of calcium with fairly sharply defined borders. At autopsy, the bile ducts were irregularly dilated, cystic and filled with friable material and irregular calculi. There was a moderately well differentiated bile duct adenocarcinoma which contained small amorphous irregular calcifications.

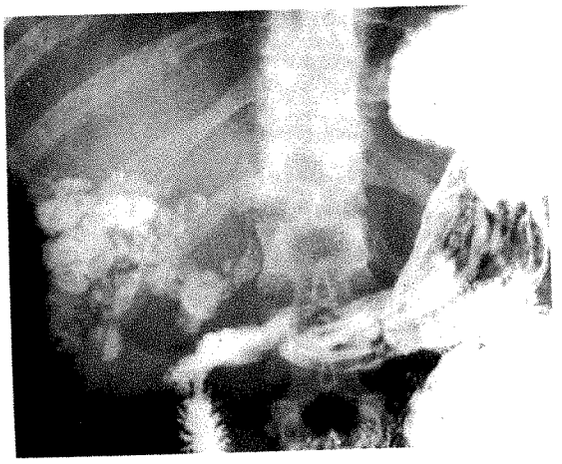


Fig. 3. Upper gastrointestinal study on January 24, 1965. Extensive hepatic calcification with normal appearance of the upper gastrointestinal tract.

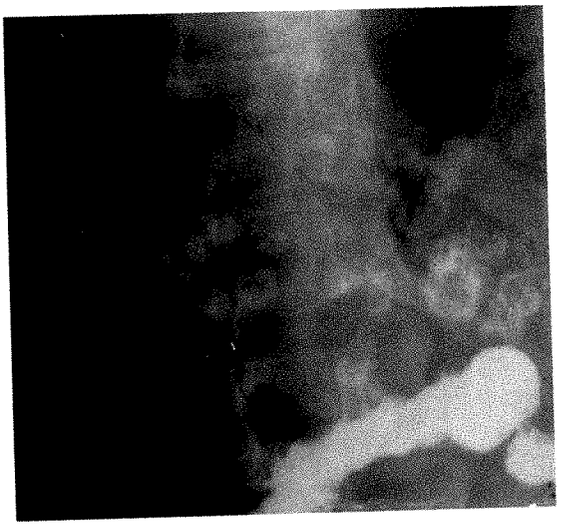


Fig. 4. Oblique gastrointestinal roentgenogram on January 24, 1965 showing the distribution of the calcification to better advantage.

In our case, how much of the calcification represented dystrophic calcification in necrotic tumor and how much represented large calculi in dilated bile ducts was difficult to determine. The spherical shape and the distribution of the calcifications suggested the presence of a considerable number of large calculi. However, at autopsy, the pathologist thought that most of the calcification was in the main tumor mass and represented dystrophic calcification in necrotic tumor tissue.

It is interesting to speculate on how long this patient had his carcinoma before he died. In a series of 62 cases of carcinoma of the liver reported by Gustafson,[2] the average course from the first symptom to death was 3.2 months, the average duration being longer in the bile duct cell type than in the liver cell type. We do know that our patient had extensive liver calcification 16 months before death. His clinicians feel that his episodes of venous obstruction were related to the liver carcinoma. Symptoms suggestive of venous obstruction

dated back at least 10 years prior to his death, which would be an unusually long survival for this disease. The large amount of calcification might be indicative of the fact that this patient did have his disease for a long period of time.

SUMMARY

1. A case is reported of a bile duct carcinoma with more extensive calcification than has previously been described in a primary liver carcinoma.

2. Many radiologists consider calcification as a sign of chronic inflammation as when found in the lung. Although hepatic calcification is rare, when present, the possibility of malignancy is great.

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COMBINED PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY AND ANGIOGRAPHY IN THE EVALUATION OF OBSTRUCTIVE JAUNDICE*

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THE cause of jaundice, whether it be primary liver parenchymal disease or biliary tract obstruction, cannot be adequately investigated by conventional roentgenologic methods at present available. Percutaneous transhepatic cholangiography (PTC) and angiography have, therefore, become valuable diagnostic procedures in spite of certain risks attending their use.[3–7] Since PTC and angiography reflect changes in related, but anatomically distinct, structures, a combination of the two procedures should be helpful in the evaluation of difficult cases. Thus, among the patients investigated because of obstructive jaundice at the Roentgendiagnostic Department, University of Lund, both PTC and selective angiography have been performed in 6. A comparison of the findings of the two procedures in these patients and an evaluation of the combined approach in the evaluation of the jaundiced patient is presented.

REPORT OF CASES AND ROENTGENOLOGIC FINDINGS

CASE I. A.I. (coe 724), a 57 year old man, had been operated upon 5 years previously because of an ampulla of Vater carcinoma which had occluded the common duct. A total pancreatectomy had been performed with choledochojejunostomy, gastrojejunostomy, and splenic resection. Postoperatively, the patient did well and his jaundice disappeared. When readmitted 5 years later, he had fever, light stools, weight loss, epigastric pain, and recurrence of his jaundice.

Selective celiac angiography (Fig. 1*A*). Tumor vessels were seen in the hilus of the liver and branches of the hepatic artery were infiltrated in this area. The size of the tumor appeared to be approximately 3×4 cm. with the central portion in the hepatoduodenal ligament. The vascularity of the liver was markedly increased, but no liver metastases were seen.

PTC (Fig. 1*B*). The proximal common duct was occluded and the intrahepatic ducts were widely dilated.

Roentgenologic diagnosis. Recurrent tumor.

At surgery, a tumor approximately 4 cm. in diameter was found to infiltrate the common duct. No resection was possible, but a new choledochojejunostomy was performed above the tumor. No liver metastases could be palpated. Pathologic examination of a biopsy revealed adenocarcinoma, similar in appearance to the original lesion.

Comment. The PTC could have been interpreted as representing either recurrent tumor or benign stricture secondary to the previous surgery. The angiographic demonstration of a well-circumscribed mass of tumor vessels just distal to the common duct occlusion as outlined by the PTC made it apparent that the patient's carcinoma had recurred.

CASE II. E.N. (coe 669), a 54 year old man, was admitted to his local hospital because of jaundice 12 years after a cholecystectomy for cholecystitis. At laparotomy, a large tumor was thought to invade the common duct from the head of the pancreas. Since the tumor was considered to be unresectable, no biopsy was taken. The patient was transferred to the University Hospital in Lund.

Combined celiac-superior mesenteric angiography (Fig. 2*A*). The proper hepatic artery was markedly displaced cranially. The middle portion of the pancreaticoduodenal arcade and its branches were irregularly narrowed and tumor

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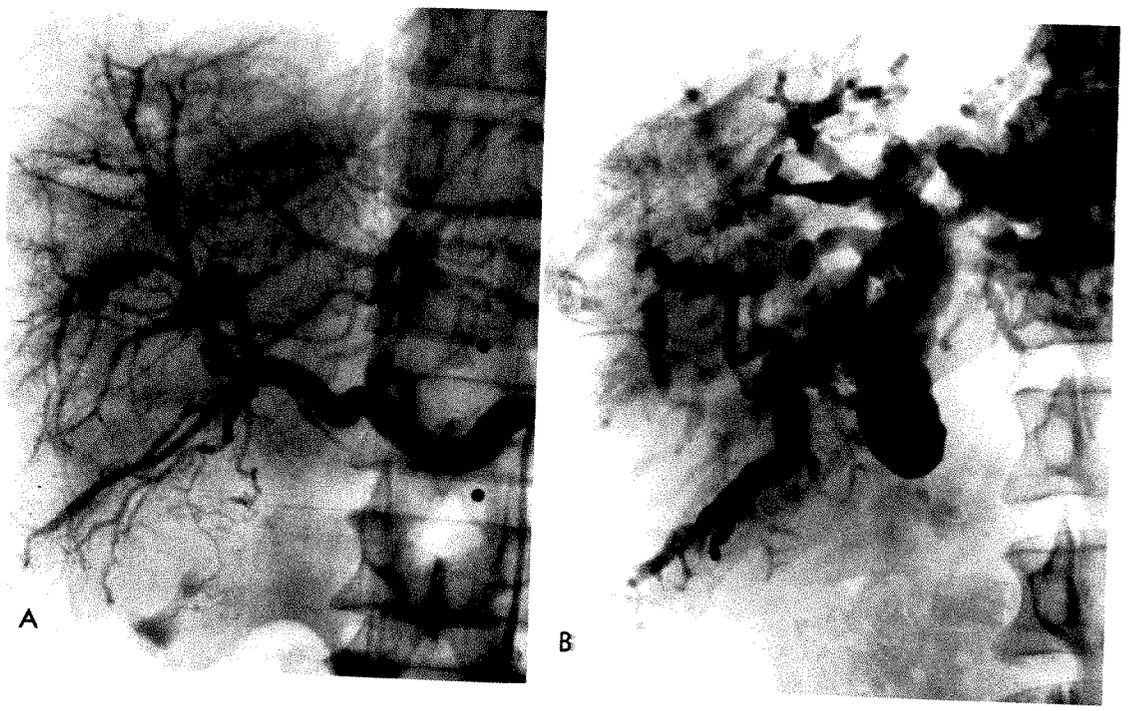




FIG. 1. Case I. Recurrent carcinoma of the ampulla of Vater. (*A*) Selective celiac angiogram in the anteroposterior position. The gastroduodenal artery has been ligated near its origin at previous surgery. Infiltrated vessels and tumor vessels are seen in the region of the hepatoduodenal ligament. (*B*) Percutaneous transhepatic cholangiogram (PTC) in the anteroposterior position. A smooth occlusion is present in the proximal common duct. Sufficient duct remains proximal to the occlusion to permit choledochojejunostomy. (*C*) Superimposition of the angiogram and PTC. The region where the tumor was seen on the angiogram corresponds well to the duct occlusion seen at PTC.

vessels were seen in the head of the pancreas. The portal vein was displaced cranially, but was not invaded by tumor. No metastases were identified in the liver.

PTC (Fig. 2*B*). The intrahepatic ducts were widely dilated, and the hepatic and common ducts were dilated to 5 cm. The distal common duct was irregularly occluded.

Roentgenologic diagnosis. Carcinoma, localized to the head of the pancreas.

At surgery a 5×5×3 cm. mass was found in the head of the pancreas. No metastases were found and a pancreatectomy was performed. Pathologic examination of the specimen revealed pancreatic carcinoma.

Comment. The hepatic artery displacement seen at angiography was thought to be secondary to the extension of avascular tumor into the liver hilus. The PTC not only localized the level of the biliary occlusion, but also demonstrated that the dilated extrahepatic ducts had caused the hepatic artery displacement. An analysis of both studies revealed the tumor to be localized to the head of the pancreas.

CASE III. I.A. (coe 758), a 50 year old woman, had been hospitalized in the department for infectious diseases for 1 month because of high fever, diarrhea, and abdominal pain. During this time she developed jaundice, light

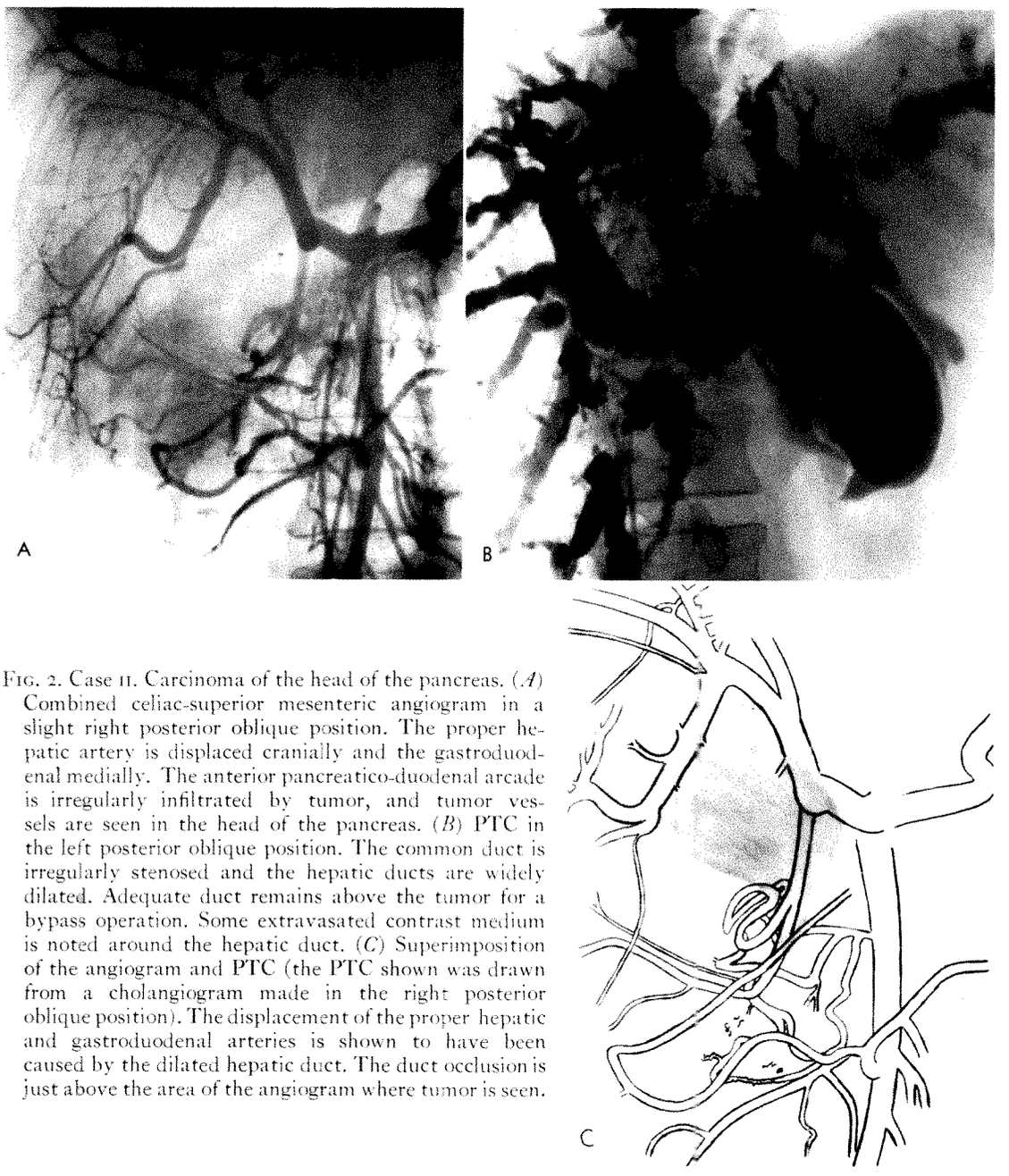


Fig. 2. Case 11. Carcinoma of the head of the pancreas. (*A*) Combined celiac-superior mesenteric angiogram in a slight right posterior oblique position. The proper hepatic artery is displaced cranially and the gastroduodenal medially. The anterior pancreatico-duodenal arcade is irregularly infiltrated by tumor, and tumor vessels are seen in the head of the pancreas. (*B*) PTC in the left posterior oblique position. The common duct is irregularly stenosed and the hepatic ducts are widely dilated. Adequate duct remains above the tumor for a bypass operation. Some extravasated contrast medium is noted around the hepatic duct. (*C*) Superimposition of the angiogram and PTC (the PTC shown was drawn from a cholangiogram made in the right posterior oblique position). The displacement of the proper hepatic and gastroduodenal arteries is shown to have been caused by the dilated hepatic duct. The duct occlusion is just above the area of the angiogram where tumor is seen.

stools, and dark urine, and was transferred to the surgical department for further investigation.

Selective celiac angiography (Fig. 3*A*). A widened cystic artery supplied tumor vessels to a 4×6 cm. mass which extended from the cranial border of the gallbladder to the liver hilus. Branches of the cystic artery were infiltrated by tumor. A metastasis was seen in the intermediate portion of the liver.

PTC (Fig. 3*B*). The right intrahepatic bile ducts were markedly dilated behind a severe stenosis of the right hepatic duct. Contrast medium passed the stenosis to a normal sized common duct, but the left intrahepatic ducts were not demonstrated.

Roentgenologic diagnosis. Primary gallbladder or hepatic duct tumor, extending into the liver hilus. Liver metastasis.

The patient was considered a poor operative risk and no surgery was performed.

Comment. Because of the rich blood supply

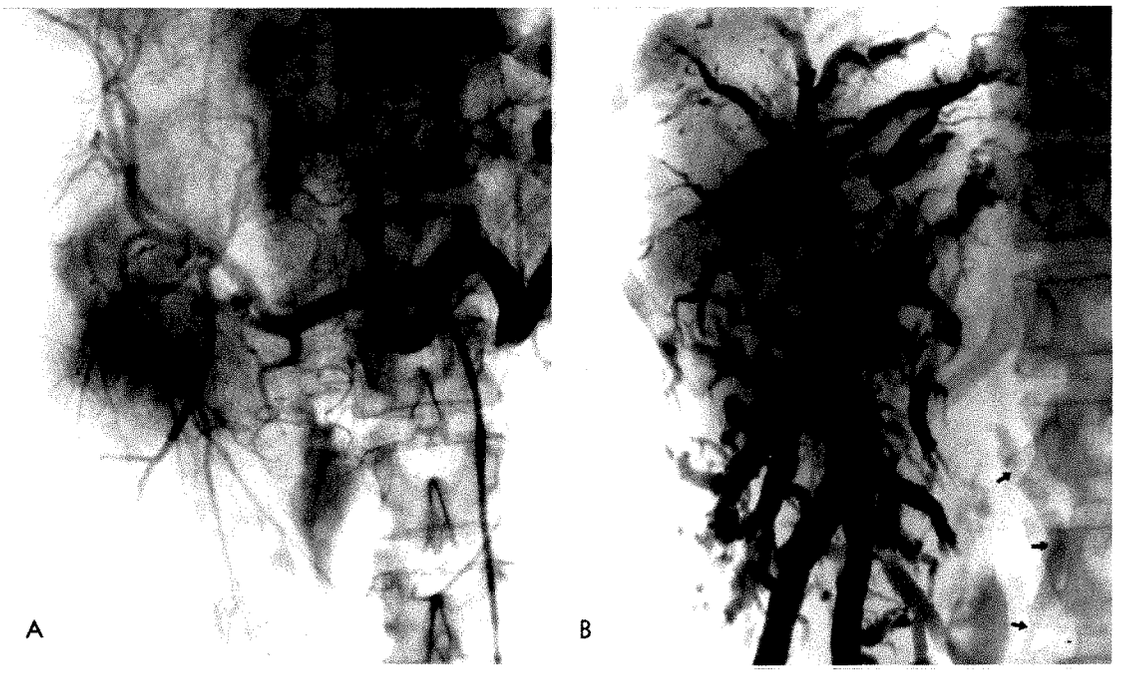
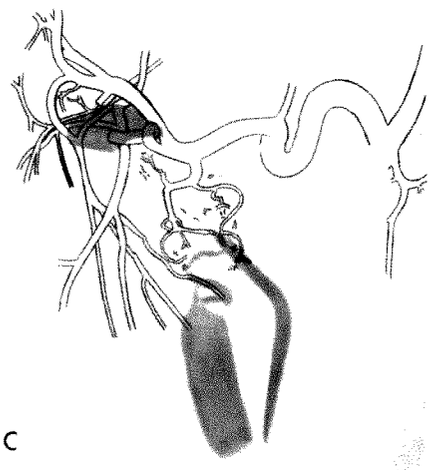


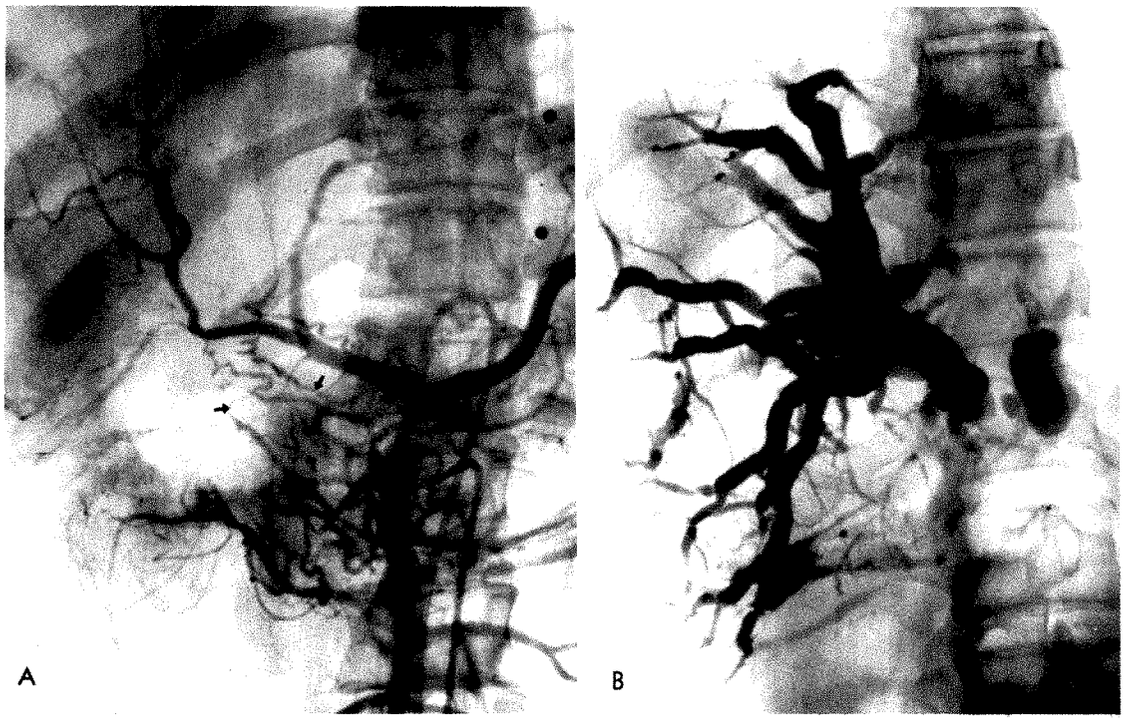
FIG. 3. Case III. Carcinoma of the gallbladder or bile ducts. (*A*) Selective celiac angiogram in the anteroposterior position. Branches of the widened cystic artery are infiltrated by tumor, and tumor vessels are seen as high as the liver hilus. The gastroduodenal artery does not fill in this projection, although it has a normal appearance in the oblique series. The gallbladder remains opacified from the previously performed PTC. (*B*) PTC in the anteroposterior position. Some contrast medium outlines a normal sized common duct (→) distal to the partial occlusion of the right hepatic duct. No filling is seen of the ducts of the left lobe of the liver. (*C*) Superimposition of the angiogram and PTC. The area of abnormal vessels corresponds well to the bile duct obstruction.



to the tumor from the cystic artery, it was possible to identify the tumor's origin. Angiography, moreover, revealed the extent of the tumor growth and the presence of a liver metastasis. From the PTC appearance of the hepatic duct stenosis, it would have been difficult to differentiate between tumor and benign stricture. The PTC revealed the ductal anatomy, however, demonstrating that no bypass operation was feasible.

CASE IV. A.J. (coe 640), a 40 year old woman, was admitted to her local hospital because of cholecystitis. At surgery, a large tumor was discovered invading the gallbladder, duodenum, omentum, and hepatic flexure of the colon. The tumor was considered to be unresectable. Six months later she returned because of gastric obstruction. She was re-explored and a gastrojejunostomy was performed. Pathologic examination of a biopsy revealed poorly differentiated carcinoma. One month after the second operation she developed jaundice, light stools, and dark urine, and was transferred to the University Hospital in Lund.

Selective superior mesenteric angiography (Fig. 4*A*). The celiac artery was completely occluded. Wide, tortuous vessels had developed to supply



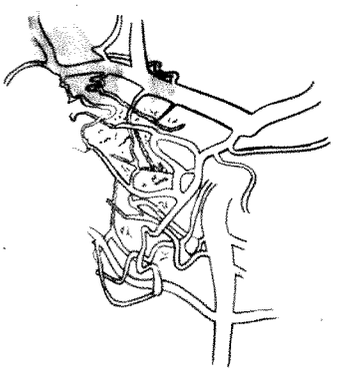


FIG. 4. Case IV. Large carcinoma in the region of the head of the pancreas of uncertain origin. (*A*) Selective superior mesenteric angiography in the anteroposterior position. The celiac artery is occluded and a rich collateral supply has developed from the superior mesenteric artery. Several of the collaterals are infiltrated by tumor (→). Tumor vessels are seen from the head of the pancreas to the liver hilus. (*B*) PTC in the left posterior oblique position. Some contrast medium passes the irregular right hepatic duct stenosis into the left ducts. No contrast medium passes distal to the liver hilus. (*C*) Superimposition of the angiogram and PTC. A large number of tumor vessels is seen at the confluence of the right and left hepatic ducts, where the occlusion is demonstrated at PTC.

the celiac circulation from the superior mesenteric artery. Tumor vessels were seen in a wide area from the head of the pancreas to the liver hilus, and some of the collateral vessels were infiltrated. The portal vein was normal and no liver metastases were seen.

PTC (Fig. 4*B*). The right intrahepatic ducts were widely dilated behind a severe stenosis of the right hepatic duct. Some contrast medium passed the stenosis to the left intrahepatic ducts, which were also dilated. No ducts were filled distal to the liver hilus.

Roentgenologic diagnosis. Large tumor of uncertain origin extending from the head of the pancreas to the liver hilus.

No surgical procedure was considered feasible.

Comment. In addition to demonstrating the size of this tumor, angiography demonstrated the possibility of operative complications secondary to removing the collateral circulation to the liver. The configuration of the hepatic duct obstruction at PTC also revealed a tumor, but gave no indication of its size. The demonstration of the ductal anatomy, however, showed that no bypass operation was possible.

CASE V. A.J. (Roe 790), a 65 year old man, was admitted to his local hospital because of right upper quadrant pain, light stools, and





FIG. 5. Case v. Primary hepatic carcinoma. (*A*) Combined celiac-superior mesenteric angiogram in the right posterior oblique position. Many infiltrated branches of the left hepatic artery are seen in the liver hilus. (*B*) PTC in the right posterior oblique position. Contrast medium passes the irregular right hepatic duct stenosis to the left hepatic duct and common duct. The filling defect in the common duct below the long hepatic duct stenosis was not seen on other roentgenograms. An inadequate duct remains above the stenosis for a bypass operation. (*C*) Superimposition of the angiogram and PTC. The tumor vessels occur in a localized area corresponding to the duct stenosis.

jaundice. Gall stones were seen at roentgen examination. He was treated conservatively and his pain disappeared. He returned to the hospital 5 months later, however, with severe jaundice. A cholecystectomy was performed, and an operative cholangiogram demonstrated a stricture 1.5 cm. long in the hepatic duct with widely dilated ducts proximally. A T-tube was left in place above the stricture. One month later a repeat T-tube cholangiogram demonstrated that the stricture had progressed. The patient was transferred to the University Hospital in Lund.

Combined celiac-superior mesenteric angiog-

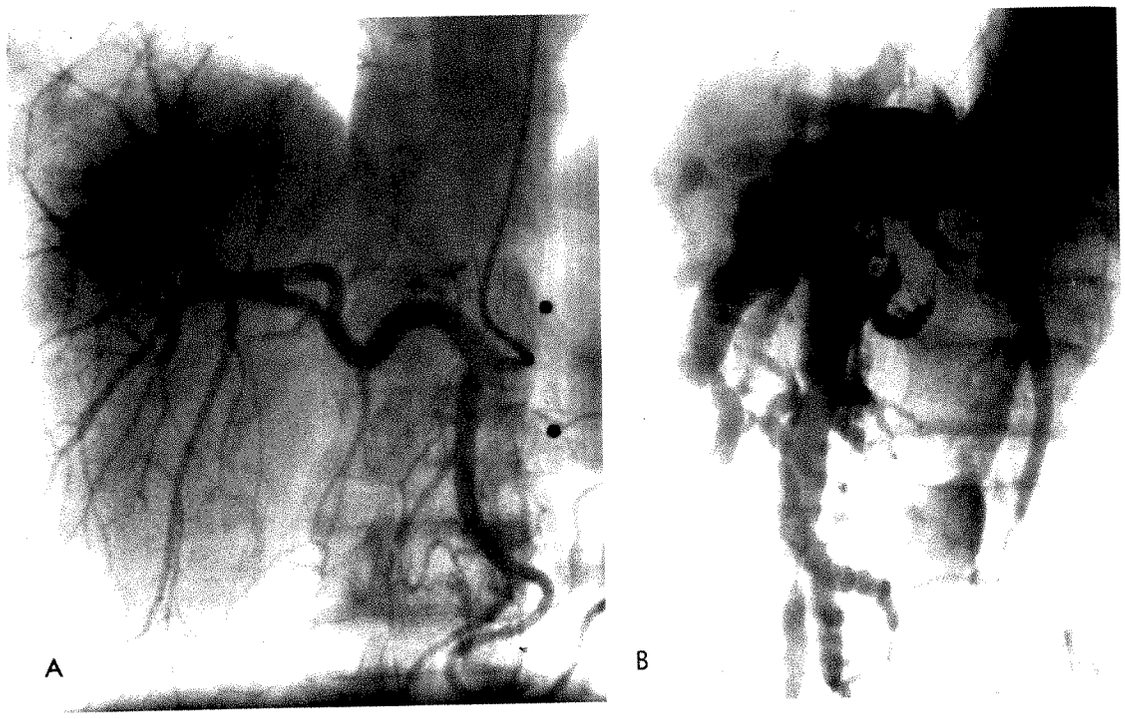




Fig. 6. Case VI. Benign stricture of uncertain etiology. (*A*) Selective hepatic angiography in the right posterior oblique position. No tumor can be seen. (*B*) PTC in the right posterior oblique position. Contrast medium passes the smooth right hepatic duct stenosis into the common duct. The intrahepatic ducts are markedly dilated. (*C*) Superimposition of the angiogram and PTC. No tumor vessels can be found at the area of obstruction.

raphy (Fig. 5*A*). Many tumor vessels were present in the hilus of the liver and branches of the left hepatic artery were infiltrated. A branch of the right hepatic artery was displaced around the tumor. The liver was markedly hypervascular, but no liver metastases could be identified. The portal vein was uninvolved by the tumor.

PTC (Fig. 5*B*). An irregular stenosis nearly occluded the right hepatic duct. The stenosis extended along the hepatic duct for a length of 3 cm., and contrast medium passed the stenosis to a normal sized common duct.

Roentgenologic diagnosis. Tumor localized to the liver hilus, probably a primary hepatic duct carcinoma.

At surgery, a tumor was palpated with its lower margin in the liver hilus. The tumor was unresectable, and a T-tube was left in place in the right hepatic duct. A biopsy taken from the wall of the hepatic duct revealed only chronic inflammatory changes.

Comment. In spite of the biopsy results, both the PTC and the angiography confirmed the surgeon's impression that the obstructive lesion was a tumor. Although the diagnosis

could have been established from either study alone, both were important in this patient, the angiography giving the extent of the tumor and the PTC demonstrating the ductal anatomy.

CASE VI. A.N. (coe 586), a 60 year old man, was admitted to the hospital because of light stools, dark urine, jaundice, and fatty food intolerance. For several years he had had a recurrent duodenal ulcer. Several days after admission he was explored. The liver was normal in size and consistency. A cholangiography, performed through the wall of the gallbladder, demonstrated no filling of the intrahepatic ducts, but no abnormality could be palpated at the apparent obstruction. A biopsy revealed chronic stasis and pericholangitis. He was transferred to the department for infectious diseases and treated with steroids, but the jaundice progressed.

Selective hepatic angiography (Fig. 6*A*). Hepatic vascularity was markedly increased, but no tumor could be found.

PTC (Fig. 6*B*). The hepatic ducts were dilated behind a stricture of the confluence of the right and left hepatic ducts. The stricture was approximately 3 cm. long and extended from the distal intrahepatic ducts to the proximal common duct. The distal common duct appeared normal.

Roentgenologic diagnosis. Benign stricture.

He has since been followed in the department for infectious diseases for about 1 year, and has remained the same clinically.

Comment. The absence of any abnormality at angiography reinforced the PTC impression that this was a benign stricture. Moreover, the PTC showed that a bypass operation was not feasible.

DISCUSSION

The exact cause of obstructive jaundice is important but often difficult to ascertain. Selective celiac and hepatic angiography have been useful in differentiating between the causes of obstructive jaundice. Fifty pancreatic or ampullary carcinomas and 20 primary liver or bile duct tumors have been demonstrated angiographically in this department.

PTC has come into use in this department in the past year. It has proved useful not only in diagnosing the etiology of obstructive jaundice, but also in defining the point of obstruction and the anatomy of the biliary ducts.

It is not the purpose of the authors to discuss the roentgenologic appearance of the different biliary obstructive processes at angiography or PTC. This has been covered adequately elsewhere.[3,4,6] It should be stressed, however, that neither method is infallible in demonstrating the cause of jaundice. The vascular distortion and formation of small collateral vessels which may follow a surgical procedure can simulate tumor, and inflammatory lesions also occasionally simulate tumors. Moreover, avascular tumors can be difficult to detect. At PTC, tumor may be impossible to differentiate from a benign stricture.

The diagnosis was made angiographically in all 5 patients who had tumor. Moreover, it was possible to state the origin of the tumor in 4 of the 5 patients because of the origin of the supplying vessels. The tumor in the fifth patient had invaded so extensively that vessels supplied it from many sources. From the angiographic findings, it could also be stated that 3 of the tumors were unresectable because of invasion of liver parenchyma around the liver hilus.

The identification of liver metastases is an important part of every celiac angiography. If metastases can definitely be demonstrated, as in 1 of the patients in this series, the patient's incurability can be stated. The inability to demonstrate a metastasis, however, does not exclude its presence.[2]

The appearance of the bile duct stenoses at PTC was definitely that of tumor in 2 of the patients. In the other 3 patients with tumor, the appearance was not so definite, but was considered to represent tumor. The appearance of the PTC in the patient with the benign stricture suggested this diagnosis. A diagnosis could be made, therefore, in 3 of the cases. Every PTC, however, gave valuable information about the location and degree of the duct stenosis and the anatomy of the proximal ducts for plan-

ning resection, T-tube drainage, or bypass surgery.

The complementary nature of these examinations in revealing both the vascular and bile duct anatomy is the primary reason for performing both in a patient who will be operated upon. In some cases in which the etiology of the bile duct obstruction is not certain from one study alone, the performance of the other can frequently give the diagnosis. The superimposition of the examinations can delineate the area on the angiogram where tumor vessels should be, if any are present.

An interesting finding at angiography was the normal appearance of the portal vein, even with extensive tumor growth in the liver hilus. This same finding was previously observed in a patient with a cholangio-cellular carcinoma of the liver.[1] A common finding in pancreatic tumors and tumors of the bile ducts is an early, irregular stenosis of the arteries, while the veins are unaffected or slightly displaced.[5] Arterial changes, therefore, seem not to be caused by local constriction by the tumor, since the veins should be constricted before the arteries. A possible cause of the arterial irregularities observed is the growth of tumor along the lymphatics of the arterial walls.

The increased arterial supply to the liver in these patients with obstructive jaundice is similar to that seen in patients with portal vein thrombosis but with a normal liver. It is different from that seen in portal cirrhosis, in which the widened arterial branches become tortuous and abruptly change in caliber.[1] The reason for increased arterial blood supply in obstructive jaundice is not clear but may be related to decreased blood flow through the portal vein.

SUMMARY

Combined angiography and percutaneous transhepatic cholangiography in the evaluation of obstructive jaundice give important information about vascular and bile duct anatomy not available from one study alone. Correlation of both studies can reveal the etiology of the obstruction in detail.

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INADVERTENT GASTROILEOSTOMY*

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PATIENTS with peptic ulcer who complain of persistent or new symptoms following a surgical procedure involving the stomach are occasionally found to have had an inadvertent anastomosis of a stomach to ileum rather than stomach to jejunum. This error, if uncorrected, almost always results in severe disability and eventually death. An analysis of reported cases indicates that while the error is almost always unsuspected clinically, it may be diagnosed readily by roentgen study. In this paper a review of the roentgen diagnosis and clinical features of inadvertent gastroileostomy is presented and 6 new cases illustrating the classical features of the syndrome are reported.

HISTORICAL BACKGROUND

The first gastroenterostomy was performed by Wölfler[73] in 1881. Scarcely 2 years later at a meeting of the German Society for Surgery, Lauenstein[41] described the first instance of inadvertent gastroileostomy.

This error, generally referred to as "rare" or "unusual," is apparently more common than is indicated by American and British authors. It was first reported in this country by Martin and Carroll[46] in 1915. In 1917 Mercur[48] reported a case and mentioned a patient who had been operated on for correction of an inadvertant gastroileostomy by Judd at the Mayo Clinic in 1912. Judd was thus the first surgeon to correct a surgical mistake of this type. This also represents the first recorded instance of such a lesion found in this country. However, 9 autopsied cases had actually been reported in the European literature prior to 1912.[2,5,6,41,51,54,55,59,71]

There are to date approximately 135 instances of gastroileostomy reported in some detail. The actual incidence is undoubtedly higher. With very few exceptions, cases are reported by individuals other than those who performed the original operation. One may also assume that an undetermined number of patients have died with undiagnosed or unsuspected gastroileostomies and that many known instances are not reported.

After elimination of those cases in which there are insufficient or unavailable clinical data, 105 cases remain which permit adequate evaluation. These comprise 52 instances of gastroileostomy with partial gastric resection (hereafter designated as Type I) and 53 cases of gastroileostomy without gastric resection (designated Type II).

REPORT OF CASES

TYPE I. GASTROILEOSTOMY WITH SUBTOTAL GASTRIC RESECTION

CASE 1. A 55 year old white female was hospitalized for complaints of diarrhea and weight loss following an operation on her stomach 5 months previously. These symptoms appeared on the 10th postoperative day and had persisted up to the time of her entry into the hospital. She had noted undigested food in her stools immediately after meals and complained of marked swelling of her feet and legs.

There were two previous hospital admissions, 7 years and 1 year earlier. These were for episodes of melena associated with syncope. In each instance the bleeding was attributed to a duodenal ulcer demonstrated by roentgen examinations.

On admission, she appeared chronically ill. Glossitis and abdominal distention were present. There was marked pitting edema of the lower extremities extending to the level of the sacrum.

Laboratory Data. Hemoglobin 8.5 gm.; total protein, 4.8 gm. per cent with albumin 2.4 gm. and globulin 2.4 gm. The electrolytes and urine were normal. An oral glucose tolerance test re-

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vealed: fasting—112 mg. per cent; 1st specimen—97 mg.; 2nd specimen—104 mg.; 3rd specimen—112 mg.; 4th specimen—80 mg.

Roentgen Examination. An upper gastrointestinal study demonstrated an irregular loop of bowel running from the pouch of a subtotally resected stomach towards the right lower quadrant with barium partially filling the cecum. Only a short segment of the afferent loop of the anastomosis was filled (Fig. 1). The roentgen findings were considered to be characteristic of a gastroileostomy.

At operation, a gastroileostomy 6 inches from the cecum was found. A Meckel's diverticulum 6 inches proximal to the anastomosis was also present. The surgical error was corrected and the patient made an uneventful recovery.

Case II. A 35 year old white male was hospitalized for epigastric pain and intermittent vomiting of 4 weeks' duration. He was known to have had a duodenal ulcer for 11 years.

On admission, his hemoglobin was 14.5 gm.; total protein 6.7 gm. per cent with albumin 4.9 gm. and globulin 1.8 gm.

A partial gastrectomy and an anterior gastrojejunostomy were performed. An ulcer within a markedly scarred duodenal bulb was left *in situ*. Oral feedings were begun 2 days postoperatively. Six days postoperatively diarrhea began. The patient was re-admitted 1 month following discharge. At that time, he was having 2 to 4 loose bowel movements daily and had lost 7 pounds. Four days after admission undigested food was observed in the patient's stool.



Fig. 1. Case I. Upper gastrointestinal study shows a barium filled loop of ileum extending from residual stomach pouch towards the right lower quadrant with partial filling of the caput cecum.

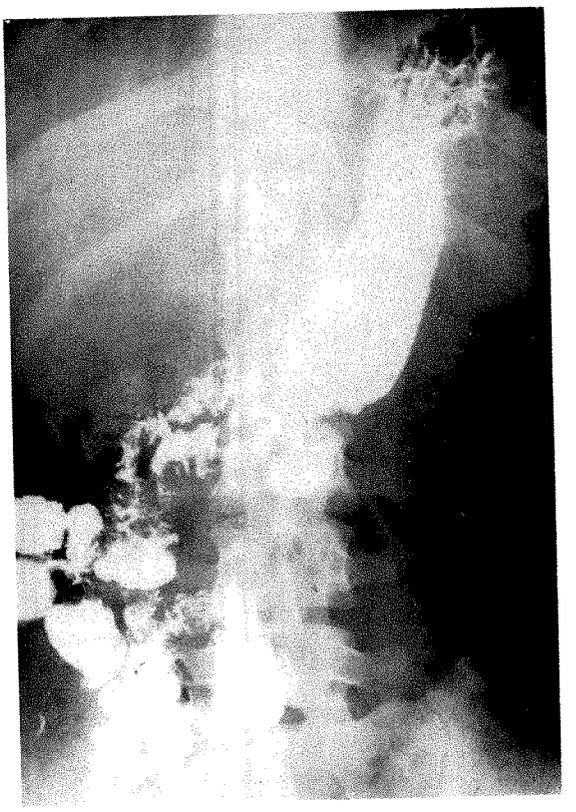


Fig. 2. Case II. A large residual gastric pouch empties into an irregularly dilated loop of small intestine in the right lower quadrant. Cecum and ascending colon are filled from this loop.

Laboratory Data. Hemoglobin, 12 gm.; total protein 6.8 gm. per cent with albumin 3.9 gm. and globulin 2.9 gm.; potassium 3.4 mEq./l.; calcium 6.8 mg. per cent. An electrocardiogram showed low T waves.

Roentgen Examination. Gastrointestinal study with orally administered barium revealed a large gastric pouch which emptied into a slightly dilated segment of bowel occupying the right lower quadrant. The cecum filled immediately from this segment (Fig. 2). The roentgen findings were regarded as typical of gastroileostomy.

Course in Hospital. The diagnosis was confirmed at laparotomy and the gastroileostomy was corrected. The patient recovered uneventfully.



FIG. 3. Case III. A short markedly dilated segment of small intestine resembling colon fills with barium from the residual pouch of a partially resected stomach. This segment communicates with the cecum. The ascending and transverse portions of the colon are partially filled.

CASE III. A 53 year old white male was hospitalized with complaints of epigastric pain and melena. He had had a similar episode 6 years previously.

Roentgen examination revealed a duodenal ulcer. Ten days after admission he underwent subtotal gastrectomy. Seventeen days postoperatively he began to have diarrhea. He was discharged 4 weeks after operation and re-admitted 11 weeks later because of intractable diarrhea. After a 3 week hospital stay he was discharged with a diagnosis of "anemia, dehydration and hypoproteinemia of undetermined origin." Roentgen studies were not done during this admission.

Six months after his original operation, he was again hospitalized because of complaints of persistence of diarrhea and a weight loss of 70 pounds.

The patient appeared pale and depleted. Physical examination was unremarkable except for evidence of weight loss and the presence of an incisional hernia.

Laboratory Data. Hemoglobin 11 gm.; fasting blood sugar 100 mg. per cent; total protein 6.2 gm. per cent with albumin 4.2 gm. and globulin 2.0 gm. The electrolytes were normal.

Roentgen Examination. Roentgen study of the upper gastrointestinal tract with orally administered barium revealed a subtotal gastrectomy with a gastric pouch of moderate size. The pouch emptied directly into a short segment of dilated small intestine constituting the efferent loop of a gastroenterostomy. This loop ran in a direct course towards the right lower quadrant, emptying into the cecum (Fig. 3). The roentgen findings were interpreted as being characteristic of gastroileostomy.

Course in Hospital. At operation, a gastroileostomy 15 inches from the ileocecal junction was found. This was corrected. Convalescence was stormy and complicated by bleeding from a vessel at the gastrojejunostomy stoma which necessitated re-exploration. The patient developed a cutaneous fistula which originated at the site of the gastrojejunostomy stoma. This was excised and the patient recovered completely.

CASE IV. A 56 year old white male was admitted to the hospital with complaints of recurrent diarrhea, weight loss of 30 pounds and marked swelling of the ankles. Four months prior to admission the patient underwent subtotal gastrectomy and gastroenterostomy for a penetrating lesser curvature ulcer of the gastric

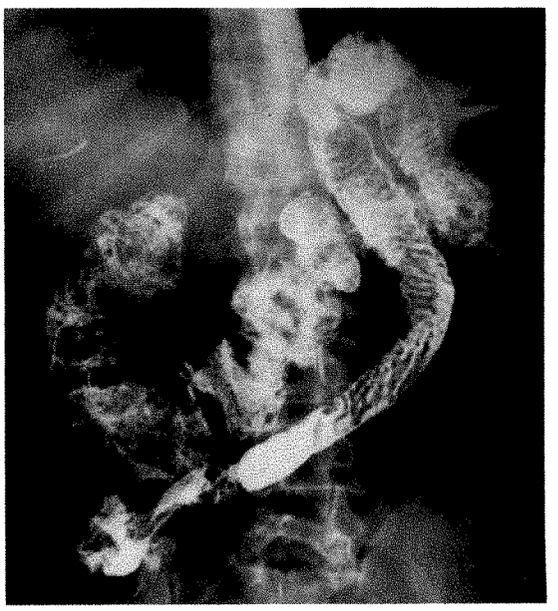


FIG. 4. Case IV. A dilated segment of intestine forms a communication between a very small residual gastric pouch and the cecum. Note the uneven filling of the transverse colon, which suggests a communication between stomach and colon.

antrum. Almost immediately after this operation, the patient began to have 8 to 10 watery, foul-smelling bowel movements daily. Weight loss ensued despite a good appetite. Ankle edema had developed 3 to 4 weeks prior to admission.

Physical examination, except for the presence of marked edema of the feet and legs, was unremarkable.

Laboratory Data. Studies of the blood were all within the limits of normal.

Roentgen Examination. A gastrointestinal series revealed a functioning gastroenterostomy with the site of anastomosis low down in the small intestine (Fig. 4). This was interpreted as representing a gastroileostomy and was confirmed at laparotomy. Correction of this error relieved the patient of his symptoms and his return to good health followed promptly.

TYPE II. GASTROILEOSTOMY WITHOUT GASTRIC RESECTION

CASE V. A 56 year old white male entered the hospital because of epigastric pain and vomiting. During a period of 10 years prior to admission, he had had 3 hospital admissions for a duodenal ulcer, confirmed by roentgen study. During the last of the 3 previous admissions, a perforated ulcer had been diagnosed and an operation on the stomach performed. One week after operation the epigastric pain and vomiting recurred and continued intermittently over the ensuing 9 months up to the time of the current admission. During this period he had a weight loss of approximately 60 pounds. There was no definite history of diarrhea.

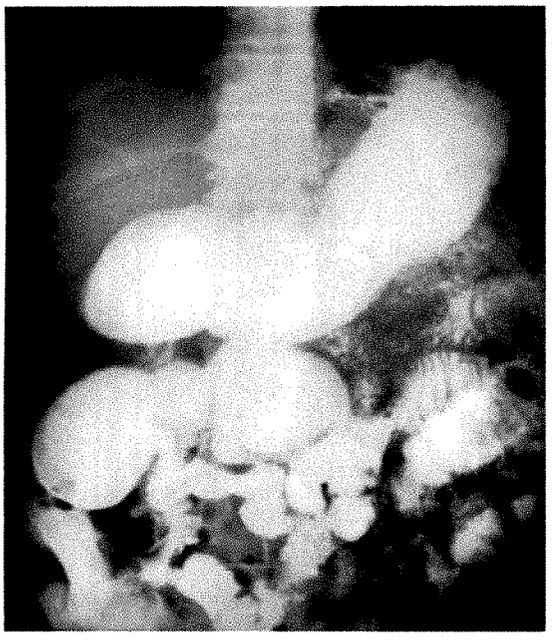


FIG. 5. Case v. There is an anastomosis at the greater curvature of the body of the stomach with a markedly dilated loop of bowel resembling colon passing to the right lower quadrant. Early filling of the cecum is noted in the extreme lower left portion of the roentgenogram (mixing of barium with fecal material). In the left upper quadrant, dilated loops of small intestine may be seen. The duodenum cannot be definitely identified.

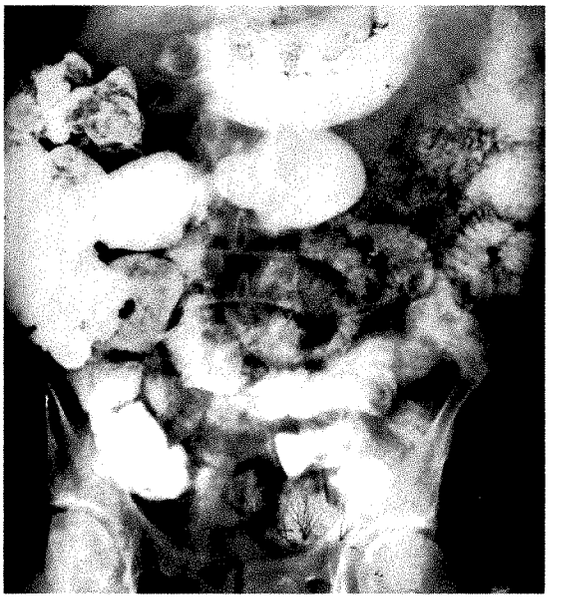


FIG. 6. Case v. Three hours after oral ingestion, there is a large volume of barium in the stomach. The cecum and ascending colon to the level of the hepatic flexure are filled but there is considerable barium in the proximal jejunum. These findings illustrate the phenomenon of cyclic refilling of the stomach.

Physical examination was unremarkable except for evident weight loss and a vertical laparotomy scar.

Laboratory Data. Studies were within the limits of normal with the exception of a cholesterol level of 102 mg. per cent.

First Roentgen Examination. Initial gastrointestinal series revealed a slightly distended, atonic stomach with retention. At the greater curvature of the stomach, there was an anastomosis of a markedly dilated loop of intestine which extended downward toward the right lower quadrant and appeared to partially fill the cecum (Fig. 5). Simultaneously, there was also filling of a number of slightly dilated small

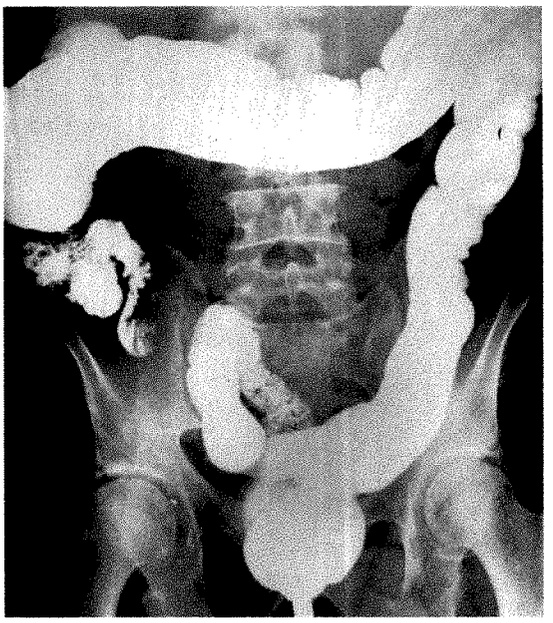


FIG. 7. Case v. Barium enema examination shows a normal colon. The terminal ileum appears normal in caliber and does not become distended as it did on the initial upper gastrointestinal examination performed 5 days previously.

intestinal loops via the duodenum which was poorly visualized. A roentgenogram made 3 hours following oral administration of the barium showed that the stomach contained a large volume of barium as did the dilated bowel segment extending towards the right lower quadrant. The ascending colon was now filled to the hepatic flexure but there was also considerable barium in the proximal jejunum (Fig. 6). These findings were tentatively interpreted as representing an anastomosis of a loop of ileum to the stomach. A gastrojejunocolic fistula was considered in the differential diagnosis. Barium enema study revealed a colon of normal caliber and position and a short segment of the terminal ileum. The visualized segment of terminal ileum was unremarkable and not dilated as was evident on the gastrointestinal examination (Fig. 7). The finding of a normal terminal ileum was puzzling and cast some doubt on the interpretation of the upper gastrointestinal examination.

Second Roentgen Examination. The stomach again showed very poor peristalsis and was dilated, containing retained food particles and fluid. Barium left the stomach via the anastomosis on its greater curvature and entered a dilated loop of bowel which passed sharply downwards into the right lower quadrant. There was a delay in filling of the duodenum and proximal small bowel on this examination. It was, however, again apparent that the duodenum and proximal small intestine were filling via the pylorus. At the 3 hour interval, the barium in the stomach became very dense (cyclic refilling). The 4 hour roentgenogram showed partial emptying of the stomach with transit of most of the barium into the distal small bowel and ascending colon as far as the hepatic flexure.

Comment. It was again evident that the distal ileum rather than the proximal jejunum was anastomosed to the stomach. There was cyclic refilling of the stomach when the portion of the barium meal leaving the stomach via the pylorus re-entered the stomach after traversing the long afferent limb of the anastomosis (Fig. 8).

Intubation Study (Fig. 9). A modified Miller-Abbott tube was passed to a point approximately 50 cm. distal to the ligament of Treitz. The balloon was inflated to prevent retrograde flow of barium. Barium was then instilled, outlining moderately dilated proximal jejunal loops. At $1\frac{1}{2}$ hours the barium reached the site of anastomosis between the small intestine and stomach and began to fill the stomach which emptied almost immediately through the pylorus and duodenum. At the same time there was also filling of the efferent limb of the gastroileostomy. This loop was dilated and had large haustra-like segmentations resembling those of the colon. Immediately after the stomach had filled by way of the pre-anastomotic loops of small intestine, loops of bowel in the left upper quadrant (jejunum) again began to fill via the duodenum (first phase of cyclic refilling). The postanastomotic loop continued to fill from the stomach and became even more dilated. At $2\frac{3}{4}$ hours the stomach was again empty but refilled completely at $3\frac{1}{2}$ hours (second phase of cyclic refilling). At this point the entire small intestine was filled with dilute barium. At $5\frac{1}{2}$ hours the stomach again refilled (third phase of cyclic refilling). At 24 hours a large portion of the barium had entered the ascending and transverse portions of the colon but there was still considerable barium remaining in the small bowel. However, cyclic refilling of the stomach was not discernible at 24 hours because of the marked dilution of the barium.

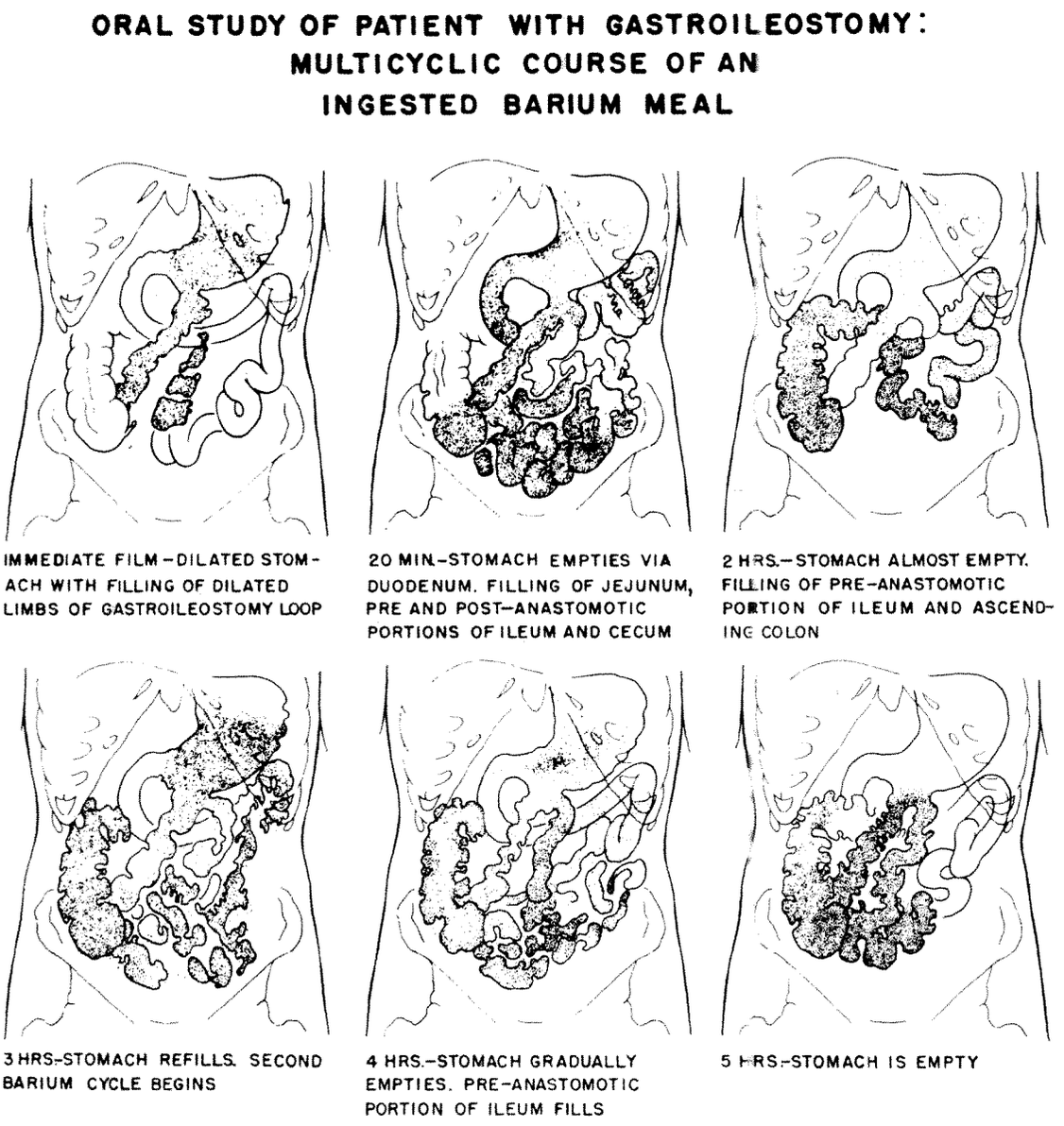


Fig. 8. Case v. Diagrammatic representation of serial roentgen study of the multicyclic course of an oral barium meal in patient with inadvertent gastroileostomy without partial gastric resection.

Nevertheless, even at 48 hours, a trace of barium was still visible in the small intestine.

Comment. Barium, introduced directly into the jejunum via a tube traversing the stomach and duodenum, demonstrated at least 3 cycles of gastric refilling. These observations also confirmed the fact that a gastroileostomy, rather than a gastrojejunostomy, had been performed 9 months earlier.

Course in Hospital. The patient continued to lose weight while in the hospital. Episodes of severe abdominal pain persisted. There was no diarrhea and microscopic examination of the stools showed no increase in fat content.

At operation, a gastroileostomy was found 3 feet from the ileocecal valve. The anastomotic stoma admitted two fingers and was indurated and edematous. A duodenal ulcer penetrating into the hepatoduodenal ligament was also present. The anastomosis was taken down and an ileo-ileostomy, subtotal gastrectomy and an antecolic isoperistaltic Hoffmeister gastroje-

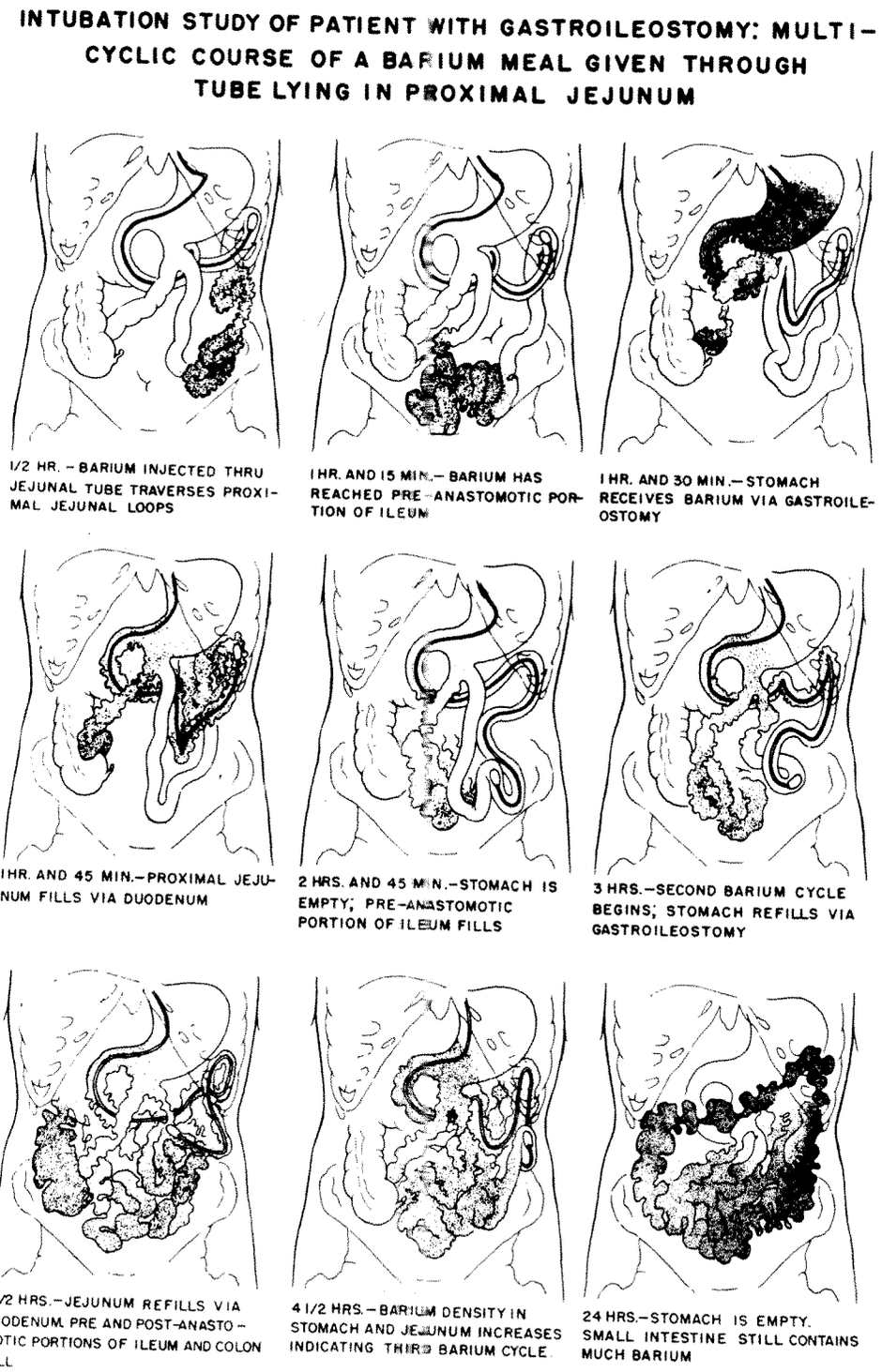


FIG. 9. Case v. Diagrammatic representation of serial roentgen study of the multicyclic course of a barium meal administered by intubation of the proximal jejunum in patient with gastroileostomy without partial gastric resection.

junostomy were performed. The patient left the hospital in good condition.

A large ulcer crater measuring 4 cm. in diameter and 0.7 cm. in depth on the iliac side of the gastroileal anastomosis was found on pathologic examination of the surgical specimen.

Summary. This 56 year old male was found to have a gastroileostomy (without gastric resection) 10 months following an operation for duodenal ulcer. Features of particluar interest in this case were: (a) cyclic refilling of the stomach, a pathognomonic sign of gastroileostomy;[12] (b) an associated iliac peptic ulcer at the stoma; and (c) absence of diarrhea or steatorrhea during the period of observation. This was attributed to intermittent malfunction of the gastroileostomy stoma (operative finding of ulceration, edema and induration of the stoma) so that the stomach contents passed predominantly through the pyloroduodenal canal.

Case VI. A 67 year old white male entered the hospital complaining of diarrhea and passage of undigested food in the stool 15 minutes after meals. These symptoms had been present for 8 months. Weight loss and vague abdominal pain radiating to the back were also noted during the same period. A significant factor elicited in the past history was that 36 years prior to this admission the patient had been operated on for a duodenal ulcer. Physical examination was not remarkable.

Laboratory Data. Except for a mild anemia, no abnormalities were found on examination of the blood. Blood proteins were not determined.

Roentgen Examination. Study of the upper gastrointestinal tract revealed passage of only a small amount of barium through an irregular narrowed pyloric channel. At the same time, a loop of small intestine leading from the stomach to the right lower quadrant and cecum was visualized. This was thought to be a gastroileostomy (Fig. 10). Calcifications in the right upper quadrant, representing gallstones, were also noted.

Operative Findings. Laparotomy disclosed a gastroileostomy 4 inches from the ileocecal valve. Because of the extreme shortness of the segment of ileum connecting the cecum and stomach, there was considerable distortion of the cecum by traction. Additional findings at operation were stones and fibrosis of the gallbladder and an actively bleeding pyloroduodenal ulcer with pyloric stenosis. There were also adhesions involving the common duct and induration of the head of the pancreas associated with an inflammatory process surrounding the duodenum. The gastroileostomy was taken down and subtotal gastrectomy and gastrojejunostomy were performed. The gallbladder was also removed. The patient left the hospital in good condition.



Fig. 10. Case VI. Visualization of gastroileostomy with cecal filling and simultaneous passage of small volume of barium through duodenum.

Comment. Inadvertent gastroileostomy had been performed 36 years prior to the onset of diarrhea and passage of undigested food in the stools. The appearance of these symptoms so many years after the original surgical error is explained by the apparent recent exacerbation of an old ulcer or the development of a new pyloric ulcer with severe pyloric channel narrowing which resulted in diversion of most of the gastric content through the gastroileostomy stoma. It is also very likely that the very short connecting segment of ileum between stomach and cecum was so distorted by traction that it never functioned well.

CLINICAL FEATURES

The symptoms of gastroileostomy are those of malabsorption and are primarily due to short circuiting of the small bowel with elimination of its digestive and absorptive functions. In brief, the clinical pic-

ture is one of starvation compounded by loss of fluid and electrolytes. The most common symptoms are diarrhea and weight loss with varying degrees of anemia, hypoproteinemia, hypokalemia, hypocalcemia, steatorrhea and avitaminosis.

Vomiting, eructations of fecal character, abdominal pain, fasting hypoglycemia with a flat glucose tolerance curve, glossitis, cheilosis, peripheral neuritis, pigmentation of the skin and buccal mucosa, purpura, low serum carotene levels,[18] poor dark adaptation and low cholesterol values are additional complaints and abnormalities encountered in these patients. Constipation is occasionally present.[46,48,49,61] Osteomalacia has been seen in 1 patient.[18] Dependent edema, ascites and even anasarca[20,62] have been reported.

The symptoms of gastroileostomy may be confused with postgastrectomy steatorrhea, the diarrhea which frequently follows gastroenterostomy with vagotomy, staphylococcic enterocolitis, gastrojejunocolic fistula, nontropical sprue, chronic pancreatitis, lymphoma of the gastrointestinal tract, regional ileitis or ulcerative colitis. Rarely, Whipple's disease, sarcoidosis, amyloidosis or adrenal insufficiency may be considered in the differential diagnosis.

In those patients who have undergone a partial gastrectomy with inadvertent gastroileostomy (Type I), the initial symptom, diarrhea, will occur as soon as intravenous fluids are discontinued and oral feeding is instituted. In the great majority of these patients the diagnosis can usually be established by a gastrointestinal series (Table II).

In patients who have undergone inadvertent gastroileostomy without gastric resection (Type II), a difficult diagnostic problem, frequently not immediately appreciated on roentgen study, may arise. The symptoms may be confusing since they may vary remarkably, depending upon the degree of patency of the pyloroduodenal canal or the gastroileostomy stoma. If pyloroduodenal stenosis of a high degree is present, diarrhea will occur immediately after operation since the stomach empties through the only avenue of egress, the gastroileostomy stoma, in which instance the symptoms are similar to those of Type I patients. If the ileostomy stoma does not function or functions only partially, the stomach contents will pass through the pyloroduodenal canal. The factors involved in such malfunction may be edema of the stoma in a depleted patient, a short loop of ileum unnaturally stretched and anatomically distorted to permit it to reach the stomach, or kinking of a longer loop of ileum. During these periods of malfunction of the ileostomy stoma, the patient may be relatively asymptomatic, may have no diarrhea and may gain weight. However, with each exacerbation of an *in situ* pyloric or duodenal ulcer, diarrhea and depletion may occur through the gastroileostomy stoma. For these reasons a bizarre clinical picture characterized at times by vomiting and/or diarrhea with intermittent periods of well being may ensue. Thus in Type II patients, correction of the initial operation has been done after periods as long as 32 years,[63] 25 years,[31] 23 years,[65] and 22 years.[63] Of interest in this respect is the patient of McKenzie and Robertson,[47] an 81 year old man who died following a transurethral resection. At autopsy, a gastroileostomy was found 4 inches from the ileocecal junction. The original operation had been performed 36 years previously. The patient's longevity and lack of symptoms were attributed to an intact and unscarred pylorus and duodenum.

In Type I patients, the average interval before correction was 9 months, in Type II patients, 65 months. This reflects the earlier onset and the greater severity of symptoms in the patients with partial gastrectomy.

CAUSES OF THE ERROR

The factors responsible for this error have been summarized by Michels and coworkers.[49] These are: obesity, inadequate anesthesia with resultant poor exposure, previous peritonitis with adhesive bands, congenital anomalies and confusion of the

Table I

POSTOPERATIVE MORTALITY IN 96 CASES OF INADVERTENT GASTROILEOSTOMY

	No. of Cases	Deaths	Per Cent Mortality
Type I	46	8	17.4
Type II	50	1	2.0
Total	96	9	9.4

peritoneal attachments of the terminal ileum and right colon with the ligament of Treitz.

The congenital anomalies found in 4 cases[10,25,28,52] were all alike, representing incomplete rotation of the midgut loop where the superior mesenteric vessels lie posterior to the duodenum while most of the jejunum is found in the right lower quadrant, the ileum in the left upper quadrant, and the ascending colon and cecum on the left.

MORTALITY

Of 105 patients, 18 died. Nine expired without surgical correction: 6—Type I and 3—Type II.

Corrective operation was performed on a total of 96 patients. The over-all postoperative mortality was 9.4 per cent (Table I).

The basic factor in the postoperative mortality is apparently the degree of initial depletion. Type I patients, although operated on earlier, are more severely depleted.

PREVENTION

Prevention of this error is discussed by Michels and co-workers,[49] Deaver,[23] and Marshall and O'Donnell.[45]

Deaver states that immediately after exploration, once a gastric resection has been decided upon, the anastomotic site in the jejunum should be marked by two sutures of different materials or colors at each end of the proposed jejunal stoma.

Identification of the jejunum is made by delivery of the left half of the transverse colon and upward traction on the mesocolon so that the ligament of Treitz is visualized.[49] The jejunum must be identified and palpated where it passes retroperitoneally behind the mesenteric vessels. Anatomic differences between jejunum and ileum, such as arrangement of the blood vessels, location of mesenteric fat, and differences in the caliber of the bowel, are rarely of practical value.

If the ligament of Trietz cannot be identified, an anomaly of rotation is probably present and the duodenum must be traced down to its junction with the jejunum.

ROENTGEN DIAGNOSIS

The papers of Boice[9] and Evans[27] are the sole communications in the radiologic literature describing the roentgen features of inadvertant gastroileostomy. Nevertheless, a correct preoperative diagnosis of this lesion has never been made without a correctly interpreted roentgen study.

In 32 of 38 Type I cases, the diagnosis was established by gastrointestinal series (Table II). In Type II cases, the roentgen diagnosis was established in only 21 of 43 cases. Some of these subjects were examined several times and at various institutions (1 patient 7 times) before the gastroileostomy was demonstrated. In Type II cases, the findings are often confusing since the barium may traverse both the pyloroduodenal canal and the gastroileostomy stoma. The principal roentgen findings are: an efferent loop crossing to the right iliac fossa with rapid appearance of barium in the colon. An anomalous colon situated in the left side of the abdomen should alert the radiologist to the possibility that an erroneous anastomosis is present.

In Type II cases, recycling of the barium meal is pathognomonic.[12] The reappearance of barium in the stomach was first noted by Brohée[11] but he apparently did not appreciate its significance.

In obscure cases or for confirmation of findings obtained by conventional upper gastrointestinal study, instillation of barium through a modified Miller-Abbott tube is a maneuver which may be of great value.[18]

The barium enema roentgenogram is

TABLE II

ACCURACY OF ROENTGEN DIAGNOSIS*

Type	Gastro-intestinal Series	Diagnosed	Per Cent	Not Diagnosed	Per Cent	Barium Enema Study	Diagnosed	Not Diagnosed
I	38	32	84	6	16	11	1	10†
II	43	21	48	22	52	11	3	3‡

* Fifteen cases of Ramos de Oliveira[57] are not included. Author states that there were 25 roentgenographic examinations of 15 cases, during which 12 of the cases were diagnosed.

† One diagnosed as gastrojejunocolic fistula.

‡ One diagnosed as gastrojejunocolic fistula.

rarely diagnostic even though gastrojejunocolic fistula is almost always demonstrated by the enema. In 10 Type I cases and in 10 Type II cases, the barium enema study was diagnostic in only 1 and 3, respectively. In our own patients the gastrolieostomy was not detected by barium enema study in the 1 patient on whom it was done (Fig. 7). There is apparently no tendency for the terminal ileum to dilate when it is filled in retrograde manner. On the other hand, the same terminal loop is almost invariably dilated when filled via the gastroileostomy stoma. This is probably related to the large volume of barium which enters the efferent loop of the anastomosis in a relatively short period of time. Although ulceration of the gastroileal stoma was found on pathologic examination of surgical or postmortem specimens in 5 of 52 Type I and in 13 of 53 Type II patients, there is no recorded instance of the roentgen demonstration of such an ulcer. In several patients pathologic examination revealed superficial, localized ileitis without ulceration. It is not unlikely that both these lesions could be demonstrated by roentgen study.

An explanation for the greater frequency of correct diagnosis in Type I cases probably lies partially in the fact that subtotal gastric resection became common during the realtively recent era of widespread proficiency in the techniques of diagnostic radiology. The cyclic refilling of numerous loops of bowel and the presence of barium at all levels of the gastrointestinal tract contribute to the difficulty in making the correct roentgen diagnosis in Type II cases. On the other hand, the roentgen findings in Type I cases are easily interpreted and subject to little error.

SUMMARY

Gastroileostomy as an inadvertent surgical error is probably more frequent than published reports indicate.

A review of the literature suggests that the lesion may easily be overlooked in patients who have persistent or new symptoms following operations involving the stomach.

The clinical symptoms supported by roentgen study permit unequivocal diagnosis of this lesion.

Six previously unreported cases illustrating the roentgen characteristics, clini cal features and laboratory findings are described.

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ROENTGEN FEATURES OF HODGKIN'S DISEASE OF THE STOMACH*

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HODGKIN'S disease affects the stomach either as part of an advanced generalized disease or, more uncommonly, as a solitary focus of involvement. Although clinically and roentgenologically, the stomach may appear to be the sole site of involvement, in all of the 45 cases studied at autopsy by Wahl and Hill,[10] there was evidence of Hodgkin's disease elsewhere, even if the other sites were only microscopically involved and thought to be grossly normal.

Review of the literature shows that Schlagenhaufer[7] in 1913 was the first author to describe a case of Hodgkin's disease limited to the gastrointestinal tract. Portmann *et al.*[6] stated that until 1954 only 45 cases had been described in the literature where the gastrointestinal tract was the principal or only site of detected involvement and described 6 new cases. Marshall and Adamson,[3] reviewing 2,014 cases of gastric malignancy studied at the Lahey Clinic between 1932 and 1958, found only 11 cases of gastric Hodgkin's disease. In 1952, Morris[4] described 3 cases out of 16,200 autopsies in which Hodgkin's disease was isolated to the stomach. Sherrick *et al.*[8] discovered 3 cases of Hodgkin's disease out of 72 primary gastric lymphomas seen at the Mayo Clinic between 1951 and 1960.

MATERIAL

We have reviewed the gastrointestinal roentgenograms of all patients with the diagnosis of Hodgkin's disease admitted to the Mount Sinai Hospital between 1959 and 1964. Out of 455 cases thus collected, 190 had gastrointestinal series performed either as part of a general work-up or because of predominant gastric symptoms. In 14 patients, there was roentgenographic evidence of gastric involvement by Hodgkin's disease; 10 of these were later confirmed either at surgery or at autopsy. Four cases were unconfirmed by histologic study, but represented patients with known Hodgkin's disease with ulcerating lesions in the stomach. One patient, not included in this series, with proven generalized Hodgkin's disease, presented with an ulcerating mass in the gastric antrum. Because of upper



FIG. 1. Localized form of Hodgkin's disease of the stomach. A smoothly demarcated mass occupies most of the fundus of the stomach. A large central diamond-shaped ulceration is noted within this tumor. This has the appearance of a large submucosal tumefaction.

* From The Department of Radiology, The Mount Sinai Hospital, New York, New York.

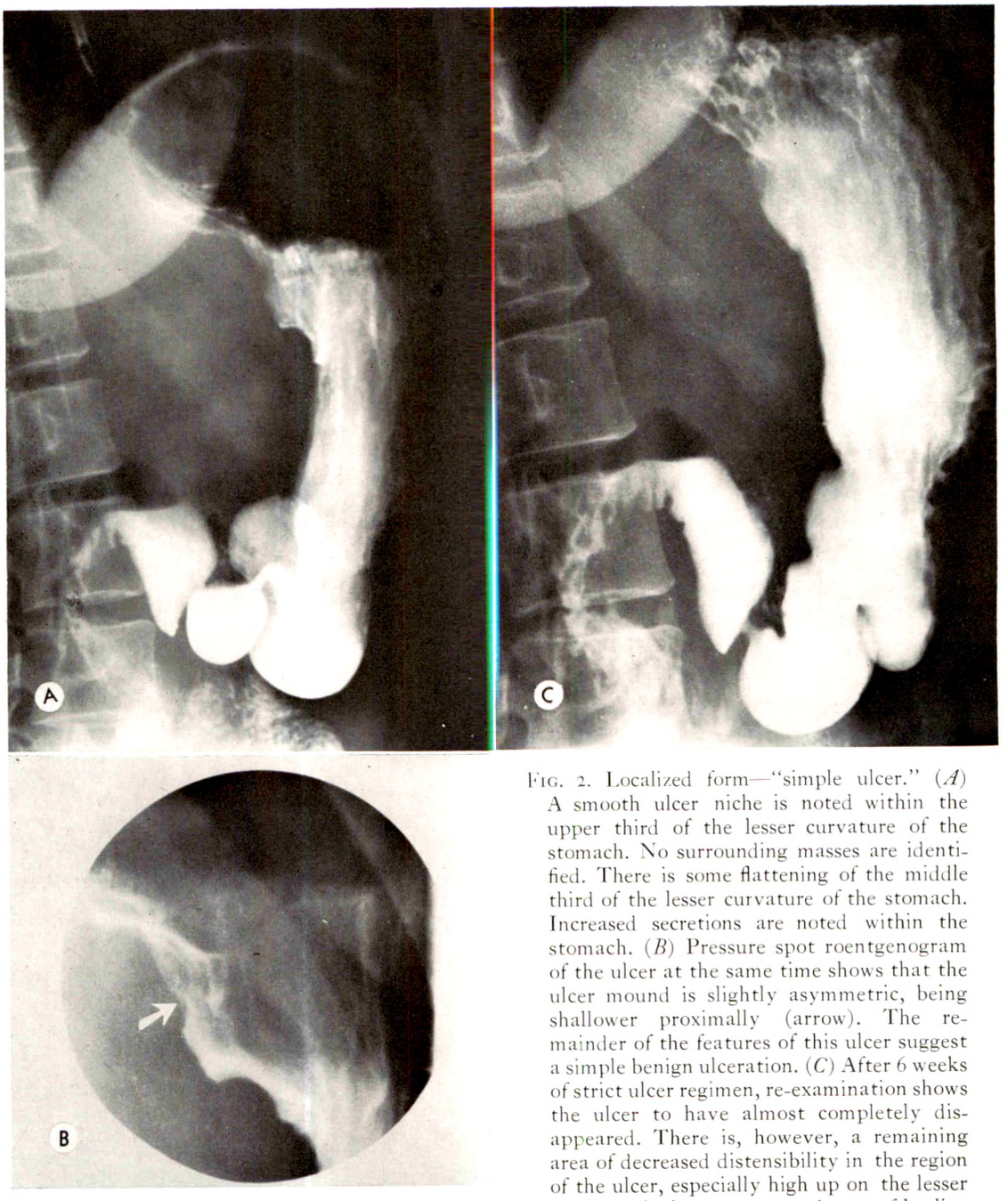


FIG. 2. Localized form—"simple ulcer." (*A*) A smooth ulcer niche is noted within the upper third of the lesser curvature of the stomach. No surrounding masses are identified. There is some flattening of the middle third of the lesser curvature of the stomach. Increased secretions are noted within the stomach. (*B*) Pressure spot roentgenogram of the ulcer at the same time shows that the ulcer mound is slightly asymmetric, being shallower proximally (arrow). The remainder of the features of this ulcer suggest a simple benign ulceration. (*C*) After 6 weeks of strict ulcer regimen, re-examination shows the ulcer to have almost completely disappeared. There is, however, a remaining area of decreased distensibility in the region of the ulcer, especially high up on the lesser curvature. A shallow crater appears to remain at this time. Although there was some degree of healing of the ulcer, the remaining deformity and shallow ulceration make the diagnosis of a simple benign ulcer untenable.

gastrointestinal hemorrhage, a gastric resection was performed, and the lesion proved to be an independent scirrhous carcinoma.

In 8 of the 14 cases in our series, the gastric lesion was the predominant or only manifestation of the disease. In the remaining 6 cases, there was generalized dis-

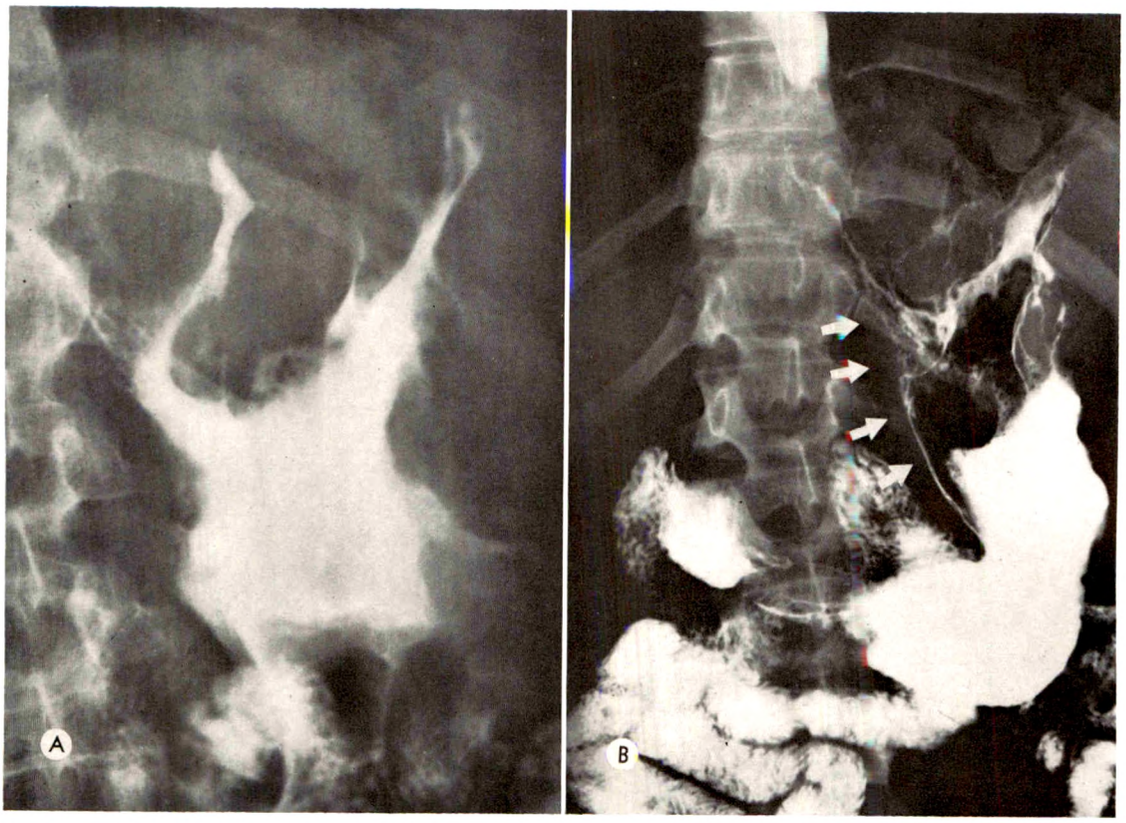


Fig. 3. Nodular form. (*A*) Barium outlines enormously thickened nodular rugal folds in the fundus of the stomach. No discrete ulcerations are noted. (*B*) In the prone projection air and barium outline the markedly altered rugal folds of the fundus of the stomach. The thickened infiltrated wall of the upper body and lower portion of the fundus of the stomach is noted along the lesser curvature (along arrows).

ease and the gastric involvement merely reflected widespread abdominal Hodgkin's disease.

ROENTGEN FINDINGS

On the basis of the gathered material, gastric Hodgkin's disease can be seen to present in the following stages of development: as a solitary intramural mass with ulceration; as a "simple ulcer;" as an infiltrating process along the rugal folds or within the gastric wall; or as multicentric gastric lesions. In far advanced cases, the disease may invade the stomach from without, originating from adjacent organs or lymph nodes.

The isolated form of gastric Hodgkin's disease presenting as a discrete intramural lesion is rarely encountered roentgenographically. Only 1 case in our series had a fundal submucosal mass with a large central ulceration (Fig. 1). None of our cases presented with a single small submucosal lesion with or without central ulceration.

The disease may present roentgenographically as a simple ulceration along the lesser curvature (Fig. 2, *A*, *B* and *C*). Although close study of the ulcer collar usually reveals it to be slightly irregular with a surrounding area of decreased distensibility, no definite submucosal or extragastric masses need be identified in relation to these ulcers. The 2 cases in our series presenting roentgenographically as "simple ulcers" were the least extensive cases with gastric involvement.

As the gastric involvement becomes more widespread, it may present as diffuse



FIG. 4. The distal half of the stomach is narrowed with maximal involvement near the antrum of the stomach. The mucosal pattern is effaced, but no actual masses or ulcerations can be delineated. Surgical clips were placed at a previous laparotomy to delineate the upper extent of the neoplastic process. The appearance in this case is indistinguishable from that of an extensive scirrhous carcinoma.

thickening, distortion and nodularity of the rugal folds usually localized in the fundus (Fig. 3, *A* and *B*). The lesion is then indistinguishable from lymphosarcoma. In these cases, there is usually no rigidity of the gastric wall or narrowing of the stomach.

When Hodgkin's disease involves the wall of the stomach without causing either ulceration or discrete nodular masses along the folds, the gross and roentgen appearance may mimic that of scirrhous carcinoma. The thickened gastric wall can sometimes be visualized between the barium outlining the inner margin and periserosal fat demarcating the external confines of the wall (Fig. 3*B*). Because of the marked desmoplastic reaction that may occur in Hodgkin's disease, the walls of the stomach become thickened and nondistensible with resulting areas of narrowing of the lumen (Fig. 4 and 5). The overlying mucosal pattern is often effaced and indistinct although no discrete ulcerations can be demonstrated. The findings are then similar to the so-called superficial spreading gastric carcinomas.

The ulcerative lesion may attain enormous size, usually with posterior penetration into a large retrogastric mass (Fig. 6). It is likely that in these cases, the disease originates in the retrogastric region with secondary involvement of the stomach. In

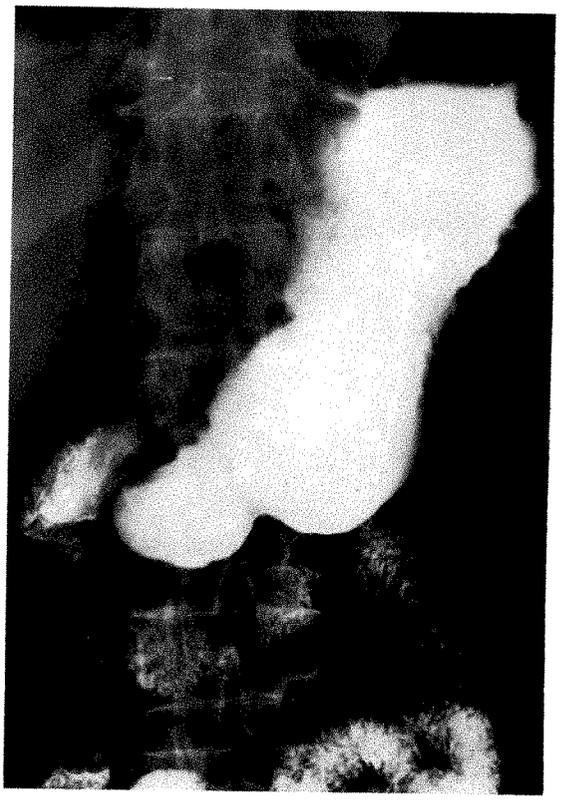


FIG. 5. There is a diffuse infiltrative process involving the lesser curvature, extending to the greater curvature along the body of the stomach. No masses or discrete ulcerations are noted. The findings are indistinguishable from those of an infiltrating carcinoma.

some instances, the ulcerative lesion presents as a Carman ulceration indistinguishable from a carcinoma of the stomach (Fig. 7).

When an irregular nodular rhomboid ulcerating lesion straddles the pylorus and extends into the duodenum, the possibility of a lymphomatous lesion should be considered in preference to carcinoma (Fig. 8).

Like all the lymphomatous diseases and unlike the usual carcinomas, Hodgkin's disease may also extend beyond the stomach into the esophagus. This was true of 3 of our cases, but in none of these instances was there roentgen evidence of obstruction at the cardia (Fig. 3, *A* and *B*; and 7). In 3 of our 14 cases, multiple lesions were seen within the stomach (Fig. 1, 7 and 9). In 1 of these, at least 4 separate lesser curvature ulcer niches were demonstrated within an infiltrated portion of the antrum (Fig. 9).

The stomach may become infiltrated by Hodgkin's disease by invasion from adjacent organs or lymph nodes. Because of the advanced stage of the disease, it is often difficult to determine the exact site of origin even at operation or autopsy. Roentgenographically, the gastric lesion is usually



Fig. 6. There is a large ulcerating lesion occupying the fundus of the stomach with retrogastric penetration. The edges of the ulcer are nodular and irregular. The region of the cardia is elevated by the surrounding mass. The mass also displaces the posterior wall of the body of the stomach anteriorly.

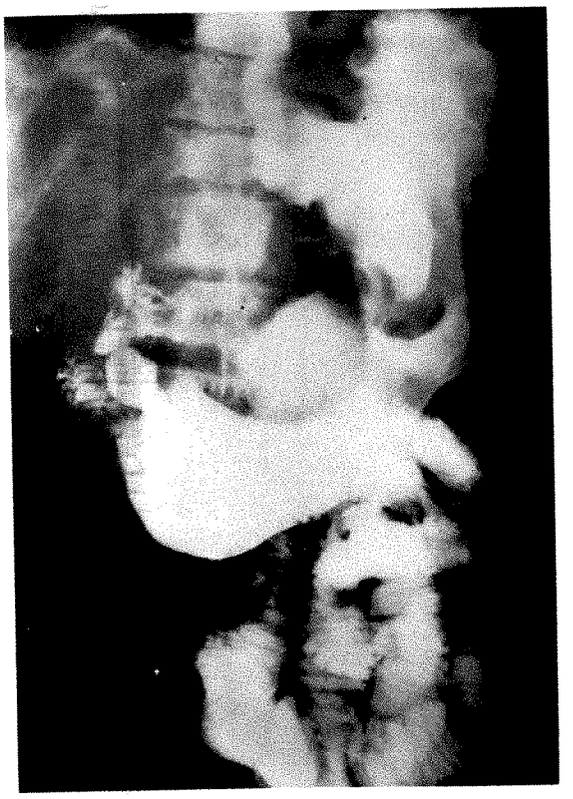


Fig. 7. There is a large ulcerating mass occupying the entire lesser curvature of the stomach. The ulcerating neoplasm presents as a Carman ulceration and is indistinguishable from carcinoma of the stomach. Only because of its enormous size and almost total gastric involvement can a lymphoma be suspected. Although the lesion extends to the cardia, there is no evidence of obstruction at the esophagogastric junction.

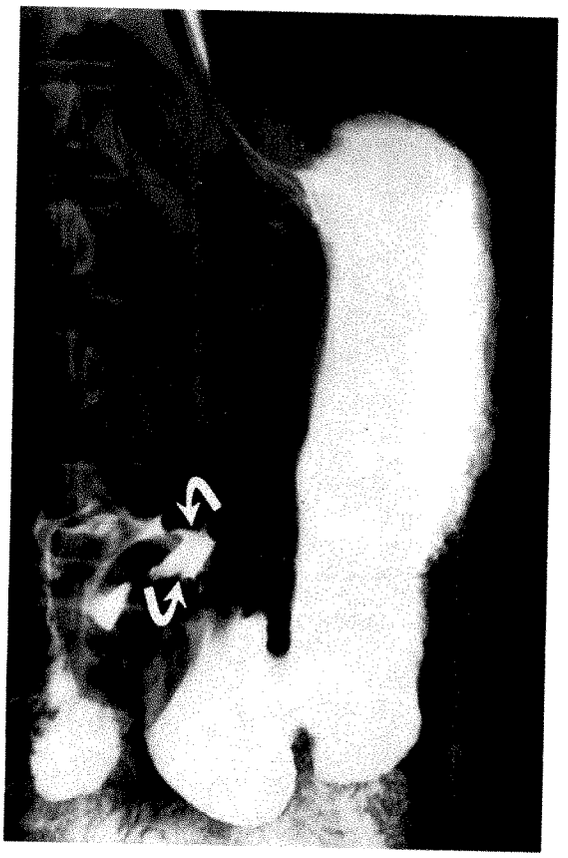


FIG. 8. There is an irregular rhomboid-shaped ulceration at the pylorus, straddling the distal antrum and proximal portion of the duodenal bulb (between arrows). There is no evidence of obstruction at the pylorus. A distinct mass cannot be outlined. Because of the irregular ulceration and peculiar shape of the ulcerative lesion, a malignant lesion should be suspected.

bulky with a large extragastric component (Fig. 10).

DISCUSSION

Although pathologically Hodgkin's disease undoubtedly starts in the submucosal lymphatics, none of our cases presented as a small isolated submucosal mass. This is in apparent agreement with the findings of Sherrick *et al.*[8] who noted that all the masses in the gastric lymphomas studied at the Mayo Clinic were large when diagnosed. The least extensive lesions in our series of gastric Hodgkin's disease presented as simple ulcerations.

Three of our cases had multicentric lesions, and we have come to regard this as the single most typical finding in Hodgkin's disease of the stomach. When there are multiple bizarre ulcerations in association with an area of decreased distensibility, the diagnosis of gastric Hodgkin's disease should be entertained, although this appearance can be mimicked by other lymphomas. The infiltrative type of Hodgkin's disease, because of its ability to invade along the gastric wall and cause a severe desmoplastic reaction, can mimic the appearance of scirrhous carcinoma of the stomach. One differential point mentioned in the literature is that the rigidity seen in scirrhous carcinoma is often lacking in Hodgkin's disease as residual peristalsis is



FIG. 9. There are at least 4 niche-like ulcerations along the lesser curvature of the stomach (arrows). This is associated with restricted distensibility of the distal portion of the lesser curvature and narrowing of the antrum. The finding of such an infiltrated area with numerous separate ulcerations suggests the possibility of a lymphoma.



Fig. 10. There is a large mass encasing the fundus of the stomach, causing invasion of the folds and a large ulceration. The mass occupies the entire left upper quadrant, elevating the left leaf of the diaphragm, and extends into the mediastinum. At laparotomy, a large exogastric mass involving the spleen, diaphragm, mediastinum and fundus of the stomach was noted.

often preserved.[2] This, however, is a subtle feature which is difficult to evaluate objectively.

When the disease involves the rugal folds without discrete ulcerations, the appearance is indistinguishable from lymphosarcoma of the stomach.

SUMMARY

We have found an incidence of 3 per cent (14 cases) of gastric involvement in 455 patients with known Hodgkin's disease who were admitted to the Mount Sinai Hospital between 1959 and 1964. In 8 of these 14 cases, the gastric lesion appeared to be the predominant or only manifestation of the disease. Gastric Hodgkin's disease was noted to occur in three main varieties: a discrete ulceration; infiltrations of the wall; or submucosal masses. In 3 of our cases, multicentric lesions were noted. The least extensive gastric lesions in our series presented as a "simple ulcer." Although no single roentgen finding is specific for gastric Hodgkin's disease, as it can be mimicked by both scirrhous carcinoma and other lymphomas, the finding of multiple ulcers within an area of decreased distensibility should suggest the diagnosis of Hodgkin's disease.

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CORROSIVE GASTRITIS DUE TO HYDROCHLORIC ACID INGESTION*

REPORT OF A CASE

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PYLORIC obstruction resulting from the ingestion of a corrosive substance has been repeatedly noted since the early report of Robert[18] in 1828. The treatment of the stenosis is a surgical problem and most of the articles describing corrosive gastric strictures appear in the surgical literature. There are numerous reports detailing the roentgenographic changes and pointing out the similarity of these changes to those found in cases of carcinoma in the stage of obstruction.[1,3,5,8,12,14,19,21]

Examination of the gastrointestinal tract usually is not obtained until several weeks after ingestion when symptoms of obstruction begin to dominate the clinical picture. A few reports demonstrating the earlier roentgenographic changes before progression to partial or complete stricture are available. Nevin *et al.*[13] reported a case in which a gastrointestinal roentgenographic examination was performed 9 days after ingestion of hydrochloric acid. A polypoid mass due to edematous folds was present in the antrum of the stomach. Later, examination revealed the typical progression to pyloric stricture and obstruction.

The case to be described also afforded an opportunity to examine the gastrointestinal tract at an early stage, at which time a large antral mass due to edema was visualized. In addition, a large ulcer crater due to erosion by the acid substance was demonstrated, making the similarity to an ulcerated gastric neoplasm even more striking in this early stage. The late changes of pyloric and antral stenosis also simulate neoplastic involvement, although there is a marked difference in appearance from the earlier changes.

REPORT OF A CASE

A 47 year old female ingested 4 or 5 ounces of hydrochloric acid (cleaning solution) in an apparent suicide attempt. She was immediately aware of very severe pain and took peptobismol and milk. A few moments later she vomited this material. When first examined, she had injection of the posterior pharynx, was hoarse and had difficulty swallowing. Intravenous fluids were given until 4 days after ingestion, at which time she began to take fluids orally. By 6 days after ingestion she was eating soft foods but still had considerable mucus production from the hypopharynx, hoarseness and dysphagia with substernal pain on swallowing. Mucosal ulceration was present in the oropharynx. Conservative treatment was continued.

Nine days after ingestion, roentgen examination of the esophagus, stomach and duodenum demonstrated a smooth mass in the gastric antrum with a 2 cm. ulcer crater. In addition, the lesser curvature of the stomach extending above the incisura angularis appeared involved by the lesion (Fig. 1). The esophagus appeared normal but the patient did aspirate a small amount of barium into the trachea (Fig. 2).

A repeat gastroduodenal examination to further evaluate the stomach was performed 2 weeks later (23 days after ingestion). At this time, the patient was asymptomatic except for continued severe hoarseness. The appearance of the stomach had changed remarkably in the 2 week period. There was now a severe constriction involving the distal portion of the body and the entire antrum of the stomach, with two small ulcer craters being present in the midportion of the constricted area (Fig. 3, *A*, *B* and *C*). There was no significant obstruction and 6 hour delayed roentgenograms showed no residual barium in the stomach. The patient rapidly developed symptoms of obstruction and an antecolic gastrojejunostomy was performed 4 days later (27 days after ingestion).

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At surgery, the wall of the lesser curvature from the cardioesophageal junction to the pylorus was markedly thickened. There was increased vascularity and external signs of inflammation of the serosa. The greater curvature proximal to the pylorus was shrunken and scarred.

DISCUSSION

In a review of the literature up to 1948, Gray and Holmes[5] found 139 cases of pyloric stenosis due to ingestion of acid corrosives. From the report of Boikan and Singer[1] it would appear that the frequency of corrosive pyloric stenosis is greater than these 139 cases would indicate. They reported 5 cases in a period of 1½ years seen at a single institution.

The ingestion of acid substances has a preferential effect on the distal stomach, resulting in progressive stenosis, usually starting 3 to 4 weeks after ingestion. Approximately 20 per cent of patients with pyloric stenosis due to acid ingestion have an associated esophageal stricture.[15,17] Alkaline corrosives have a more marked effect on the esophagus. Heindl[7] reported a 20 per cent incidence of pyloric stenosis in 116 cases of esophageal stricture due to lye ingestion.



FIG. 1. Roentgenogram 9 days after ingestion of hydrochloric acid demonstrates an antral mass due to edematous folds with a large ulcer crater. The lesser curvature also appears to be involved by a mass.



FIG. 2. Aspiration of barium with coating of the larynx and proximal trachea.

The cause of the selective effect of acid on the pylorus is probably related to its rapid passage down the esophagus and along the lesser curvature of the stomach, especially if the stomach is full at the time of ingestion. When the corrosive substance

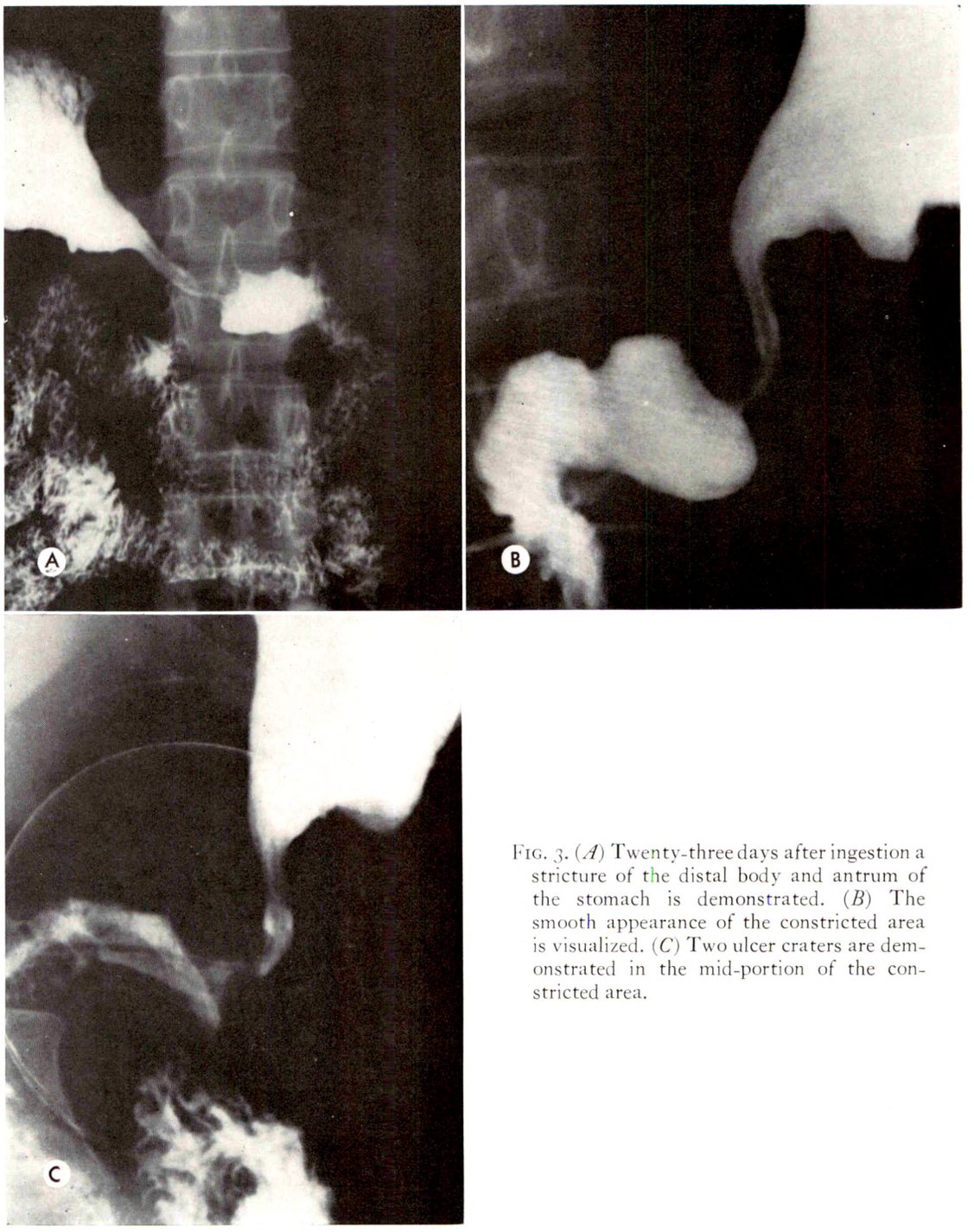


FIG. 3. (*A*) Twenty-three days after ingestion a stricture of the distal body and antrum of the stomach is demonstrated. (*B*) The smooth appearance of the constricted area is visualized. (*C*) Two ulcer craters are demonstrated in the mid-portion of the constricted area.

reaches the antrum and pylorus, tetanic contractions are set up as experimentally demonstrated by Testa.[23] The exposure in this area is, thus, prolonged, resulting in severe changes in the relatively delicate gastric columnar epithelium.

Alkaline substances are more corrosive than acid ones and, therefore, have a greater effect on the relatively resistant esophageal squamous epithelium. In the stomach, however, the normal gastric acidity has a neutralizing effect with re-

sultant sparing of this area.

Corrosive substances which have been reported to cause pyloric stenosis include hydrochloric acid,[6,8,10,12,13,19,20] sulfuric acid,[1,5,21] nitric acid,[1,14,16] acetic acid,[16] trichloracetic acid, carbolic acid, oxalic acid, lye[1] and lysol, ferrous sulfate (feosol),[2,25,26] copper sulfate, bichloride of mercury,[4] formaldehyde, [20,24] clorox, [22] zinc chloride,[12,20] ammonium hydroxide (household ammonia),[4,14] tincture of iodine and chlorine. Hydrochloric acid is the most common agent in cases resulting in pyloric stenosis. Sulfuric acid ingestion is more likely to result in early death due to perforation and gangrene.

Treatment of corrosive pyloric stenosis requires a surgical procedure to bypass the obstruction, usually without gastrectomy. Attempts at conservative therapy, avoiding surgery, are not effective.

SUMMARY

A case of corrosive gastritis due to hydrochloric acid ingestion is reported with demonstration of a corrosive ulcer with surrounding edema in the early stages. In the late stages the typical stenotic lesion with accompanying clinical symptoms of obstruction supervenes. The similarity of both stages to gastric neoplasm is stressed.

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SPONTANEOUS RUPTURE OF THE ESOPHAGUS*

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SPONTANEOUS rupture of the esophagus can be defined simply as rupture occurring in an otherwise healthy esophagus. In 1884, McKenzie[36] described the condition at greater length as "a sudden bursting of the gullet during prolonged and violent vomiting, giving rise to acute pain in the course of the tube with extreme dyspnoea, sometimes even to orthopnoea, subcutaneous emphysema and to collapse, generally ending in death."

The basic factor is that there is no preexisting disease in the esophagus to warrant rupture; in other words, it is spontaneous. By general usage, however, this strict definition is no longer rigidly adhered to and peptic esophagitis and ulceration, as etiologic factors, either singly or combined, are now included in the term. The adjective spontaneous is, therefore, incorrect and some authors suggest that it should not be accepted. It is used in this article because of the wide acceptance that it denotes the entity under discussion.

Perforation and rupture must be differentiated. Perforation is usually the result of (a) direct trauma, which includes war wounds and surgery, (b) instrumentation, which includes esophagoscopy, or (c) disease processes of the esophageal wall. This latter term includes such conditions as carcinoma, syphilis, tuberculosis, aneurysm, diverticulum, foreign body, congenital abnormality, ingestion of caustics and, of course, should strictly include peptic esophagitis and ulceration.[6,33,50] The actual defect in the wall is usually small and circular and there is no predilection for any particular site. Rupture, on the other hand, is always abrupt in onset with no previous symptoms referable to the organ, it almost always occurs at the same site and the tear is usually linear and in the longitudinal axis of the esophagus.[4,18]

In 1724, a Dutch physician, Hermann Boerhaave,[8] recorded the first case I have been able to trace in the literature. The patient was the Grand Admiral of Holland who was given to wining and dining well and who presented as a fairly typical example of the condition. He died and the postmortem findings were reported in detail. The site of the tear was about 5 cm. above the diaphragm and no inflammation was noted in the area.

Up to date, approximately 250 cases have been reported and, judging from this, the incidence is about 1 in 6,000 patients.[32] The condition is, therfore, rare and is probably not increasing, but is being more generally recognized.

We have had 4 further examples of the condition and the case histories are recorded below. The great importance of this disease lies in the fact that early diagnosis is imperative for survival and that radiology is, perhaps, the most important investigation in arriving at that diagnosis.

ETIOLOGY

The 2 main etiologic factors concerned in spontaneous rupture of the esophagus are: (1) increased intraluminal pressure, and (2) peptic esophagitis and ulceration.

Each of these factors can cause spontaneous rupture independently of the other, but they are commonly combined in an individual case. Currently, there is controversy regarding the relative importance of each of these causes. In a minority of cases, no cause has been found.

(1) Most observers contend that a tremendous and sudden increase in the pressure in an apparently normal esophagus is the usual cause of rupture.[33] This increase in pressure is due usually to vomiting or retching and sometimes to increased intra-abdominal pressure from external trauma

* Based on a paper read at a meeting of the Royal Society of Medicine, Section of Radiology, London, March 19, 1965.
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or from any other cause.[33,35] The rapidity of the increase rather than the total pressure applied is the deciding factor in producing a tear.

Vomiting is initiated by the vomiting center of the vagus in the floor of the fourth ventricle and excitation of this center is raised by dehydration, inadequate carbohydrate intake and anoxia, which conditions occur in alcoholism, confused mental states and coma.[9]

Vomiting took place in a high proportion of the reported cases. Bódi *et al.*[9] reported vomiting in 75 out of 86 patients and Anderson[4] noted it in 75 per cent of his series. It may be violent or recurrent or it may occur only once and it may be spontaneous or self-induced.

Most authors contend that the rupture occurs after a heavy meal, or after heavy consumption of alcohol,[39] and Graham, Barnes and Rubenstein[26] found an alcoholic history in 80 per cent of patients. On the other hand, Ware *et al.*[50] feel that the question of an alcoholic history is overrated; they found it in only 50 per cent in their series. Kinsella, Morse and Hertzog[31] point out that many cases had spontaneous rupture with empty stomachs and, indeed, 1 of our patients (Case 1) was a case in point. The stomach can contain big quantities without any rise in intragastric pressure but appears to be upset by an extra large intake when the pressure cannot be relieved by further distention of the organ.[9]

Partial or complete obstruction of the proximal esophagus is an important factor in causing rupture; otherwise, it is difficult to understand the rapid build-up in pressure. McKenzie[36] stated that a tear will only follow if the vomitus in the esophagus is not expelled as quickly as it is received and thus the organ distends like a blind tube and ruptures at its weakest point.

Muscular incoordination may produce obstruction of the upper esophagus and this may be due to fatigue of the vomiting center or of the muscles themselves, caused by repeated vomiting. Similar muscular incoordination occurs with the mental confusion of alcoholics. The result is that the hyoid is not held forward or that the cricopharyngeus does not relax at the critical moment. Spasm of the esophagus from regurgitation of acid gastric juice is another cause and in any of these instances failure of the diaphragm to relax is a contributory factor. The case recorded by Smead[46] is an example of the danger of repeated vomiting. His patient had gangrene of the bowel and after 2 hours of vomiting developed a tear just inferior to a stricture of the esophagus. Many similar cases have been described.[45,47]

External trauma, when leading to sudden and sharp increase in intra-abdominal and intra-esophageal pressure, is another less common cause of spontaneous rupture and cases have been reported following car and motorcycle accidents and instances where heavy weights have fallen on the abdomen. The site of the rupture is the same and although no histories of full stomachs are recorded, this was probably the case, as large quantities of gastric contents were found in the pleural cavities.

Increases in intra-abdominal pressure may also occur during labor, weight-lifting, straining, epilepsy and coughing, and indeed, spontaneous rupture has complicated each of these conditions at least once.[4,33]

(2) The weight of opinion in favor of peptic esophagitis and ulceration being the main etiologic factor in spontaneous rupture is considerable, but most authorities agree that vomiting or recurrent retching provides the final insult in an already weakened organ.[3,5,12,31] Pre-existing inflammation was confirmed in 17 out of 23 cases by Ridgway and Duncan[41] and was mentioned by Williams and Boyd.[51] Wangensteen[49] considered it to be the main etiologic factor, and reports that he has confirmed this by animal experiments. No rupture or esophagitis occurred in his animals when the acid-bearing part of the stomach had been removed.

However, in the same context, it must be mentioned that Brosch[11] incubated human esophagi in acid peptic juice with no increased weakness. Pancreatic juice and bile also have the power of causing diges-

tion of the esophageal mucosa, and regurgitation of these substances appeared to be the cause of rupture in 1 patient with a subtotal gastrectomy, which was mentioned by Cross and Wangensteen.[15]

Esophagitis and vomiting may be initiated by pyloric obstruction, which gives rise to the accumulation of gastric juice in the esophagus and results in digestion of the esophageal mucosa. Indeed, any regurgitation of gastric contents into the esophagus may remain there for some considerable time with similar effect.

Marston and Valk[35] suggest that the initial lesion is, in fact, a laceration of the mucosa from vomiting, which suppurates and erodes due to the action of the acid-pepsin in the regurgitated juice. This laceration may later rupture during a further episode of vomiting. Seybold, Johnson and Leary,[44] proposed the same sequence of events, but they believe that the resulting erosion will go on to rupture after several hours, with or without vomiting.

There is thus much support for each of the two main etiologic factors concerned, but, as previoulsy stated, both are commonly combined in any one case. However, two points might be made in favor of pressure being the principal cause. Firstly, rupture has occurred in perfectly healthy esophagi in patients suffering from seasickness, recovering from anesthetics, with small bowel obstruction, with peritoneal irritation from secondaries and with large ovarian cysts. Secondly, it could be argued that Wangensteen's[49] experiments prove only that reflux causes esophagitis but not that spontaneous rupture is necessarily due to this esophagitis, and it also must be remembered that, while esophagitis is common, spontaneous rupture is rare. In support of pre-existing inflammation is the fact that many patients had developed rupture while relaxed, *e.g.*, while reading, watching television and even during sleep. Hochberg and Parlamis[28] state that 80 per cent of cases occur in previously healthy esophagi and about 10 per cent in patients with esophagitis or ulcer.

The increased incidence of spontaneous rupture in neurologic lesions has been documented by Cushing,[16] who noted acute peptic ulceration of the esophagus, stomach, and duodenum in several cases following operations in the posterior fossa. He attributed the formation of these ulcers to stimulation of the vagal tract in the brain, with resultant local spasm of small blood vessels leading to hemorrhage or ischemia in the affected areas. Anderson[3] later found that stimulation of the tuber cinereum leads to hyperperistalsis of the stomach.

MECHANISM

The mechanism involved in spontaneous rupture of the esophagus was first experimentally investigated by McKenzie in 1884.[36] He removed esophagi from adult cadavers, tied them distally, and introduced water at varying pressures into the proximal ends. He found that the vast majority of the tears so produced were similar to those seen clinically. In over half of his cases, the muscle and mucosa gave way together; in others the muscle separated and the mucosa first bulged through and then ruptured. In all, the mucosal defect was smaller than the muscular. The pressures necessary to achieve rupture ranged from 5.75 to 11 pounds per square inch, with an average of 7 pounds per square inch. He concluded that the tears are always longitudinal, never occur in the upper esophagus and that the mucosa is more resistant than the muscle.

Later, Duval[19] and Burt[13] opened stomachs and applied pressure from below to reproduce, as closely as possible, the clinical conditions for rupture. A tube was inserted and tied into the stomach with the esophagus *in situ* and oxygen was introduced against a column of barium in the esophagus, which was watched on a screen. Rupture was experimentally produced in their cases at pressures from 3.5 to 6 pounds per square inch.

Mackler,[33] produced artificial rupture of the esophagus at an average pressure of 5 pounds per square inch. Mallory and

Weiss,[34] who clamped off the proximal end of the esophagus, produced rupture at lower pressures, that is, in the order of 2 to 3 pounds per square inch. Burt[13] estimated the mucosal resistance to be 4.09 pounds per square inch compared with a muscular resistance of 3.49 pounds per square inch.

The question of obstruction proximally is important, as less pressure will then be required to cause rupture, as shown by Mallory and Weiss.[34] Mucosal resistance may be reduced in elderly people due to mucosal atrophy and this was a point raised by Decker, Zamcheck and Mallory.[17] Anderson,[4] also considered that people over 50 years have reduced resistance to pressure, and he found that children under 12 years of age could withstand 4 times as much pressure as a normal adult. Malnutrition may also reduce the strength of the organ.

Derbes and Mitchell[18] found that there are two stresses on the esophagus, a tangential and a longitudinal, the former producing a longitudinal tear and the latter a transverse one. The tangential stress is the one commonly experienced, the longitudinal one only acting when both ends of the esophagus are occluded. Less pressure is necessary to produce longitudinal than circular tears and almost all of the tears produced experimentally were similar to those seen clinically. Duval[19] and Burt[13] recognized that the important factor is the rapidity of the increase in the intraluminal pressure rather than the actual pressure produced. It is also probable that the pressures causing rupture *in vivo* are less than those recorded experimentally, as there is a higher pressure gradient across the esophageal wall in life because of the high intraesophageal pressure and the low intrathoracic pressure during vomiting and also because most of the organs tested experimentally were removed from their supporting beds, whereas in life the pressure is concentrated on the common site of rupture mainly because the remainder of the esophagus is well supported.

Against this must be set one of the objections to the experimental results, that is, the decrease in strength of the esophageal wall after death, by autolysis.[31,33] Experimenting on dogs, Morton and Sullivan[38] found that there was a 50 per cent decrease in strength after 1 hour. The esophagi used were examined as soon as possible post mortem to obviate this difficulty, but the time of examination did vary from 1 to 22 or 31 hours in different series and, thus, this factor is of significance, although how much is difficult to estimate. A second objection was that, in some experiments at least, esophagi were removed from the esophageal beds, and, therefore, some of the normal support was not acting. Other workers left the organs *in situ*.

The common site for rupture to occur is in the left posterolateral wall of the lower end of the esophagus. During vomiting, the intraluminal pressure in the esophagus is markedly increased, but this should be evenly distributed throughout the organ. Why, then, does rupture commonly occur at this one site? There appear to be two groups of factors involved: (a) the lack of support from surrounding structures, and (b) an intrinsic weakness of the organ here.

(a) The aorta, retroperitoneal fat and, below the diaphragm, the liver tunnel and fundus of the stomach support the esophagus on the right. Posteromedially, there are the vertebral bodies; posteriorly, the vertebrae and aorta, and anteriorly and anterolaterally, the pericardium and heart. The lower end of the esophagus is also supported on three sides by connective tissue extending between the vena cava and azygos, thus leaving only one area where it is free to distend and rupture. However, the fact that this is not the whole story is shown by the experiments of Mackler[33] when, in esophagi removed post mortem from cadavers and subjected to varying intraluminal air pressures, the site of the tear was almost always at the same common site of rupture. This brings us to the second group of factors determining the site of the rupture, which is

(b) The probable existence of an intrinsic weakness of the wall in this area. The points in favor of this are:

1. There is considered to be a congenital weakness here because of the angulation between the thoracic and abdominal esophagus. Bódi *et al.*[9] considered this to be significant as it may favor temporary obstruction with resultant increase in the intraluminal pressure in this segment.

2. The smooth muscle fibers become longitudinal and terminate conically here. These conical fibers are thin and allow easy separation for the mucosa to herniate through.

3. The sites of entry of many of the vessels and nerves into the muscle tend to weaken the esophagus at the lower end.

4. Segmental defects have been found in the circular muscle fibers in some cadavers in the same area.[3]

5. The upper third of the esophagus contains cross-striated muscle fibers exclusively, while the middle third contains mixed, and the lower third contains smooth fibers exclusively.[33] This involuntary muscle is not as strong as the voluntary striated muscle.

6. Anderson[3] maintains that the esophageal mucosa at the lower end of the esophagus is weaker than that of the cardia.

PATHOLOGY

Originally, the entity of spontaneous rupture of the esophagus was disputed, for example, by Fitz[21] in 1877, who claimed that postmortem autolysis accounted for the mediastinal findings rather than rupture and thought that the surgical emphysema present was due to bronchopulmonary disruption, although none was found. Many other investigators missed diagnosing the condition even at postmortem examination as the actual tear was too small or was slit by a knife during dissection. Again, if the patient did happen to survive for some time, the necrosis and gangrene resulting so distorted the anatomy that a small perforation was easily missed.

The actual tear varies from 0.6 to 8.9 cm. in length, the average being 2.5 cm., and it is usually sited about 2.5 to 7.5 cm. above the cardia. It is always longitudinal and the mucosal defect is commonly smaller than the muscular, the mucosa being more resistant. The left posterolateral wall is most often affected and, according to Hochberg and Parlamis,[28] it occurs here in 70 per cent of cases.

The controversy as to whether the esophageal tear occurs in a normal, healthy esophagus, or in a diseased esophagus, has been mentioned. Many observers maintain that there is no evidence of inflammation prior to the rupture to be found in the pathologic specimens. They believe that the mucosal excoriation in the vicinity of the tear and the infiltration of inflammatory cells are not found unless the patient survives 12 hours and that it follows acute inflammation from the regurgitating acid gastric juice and bacterial infiltration in the mediastinum. Mackler[33] also notes that occasional scattered lymphocytes are found in the normal esophagus and also occur in cases following acute trauma, where there is no evidence of pre-existing esophageal disease. Many such traumatic cases are on record,[1,2,27,30,40,47] and, as already stated, there are many cases of spontaneous rupture occurring in patients with disease elsewhere, and with normal esophagi. The fact that the tears are usually linear and vertical supports the idea that they occur in normal esophagi, since tears that occur in an inflamed or ulcerated esophagus are irregular, sloughing and partially digested.

The similarity to the Mallory-Weiss syndrome is evident. This can be defined as gastrointestinal hemorrhage caused by multiple, small lacerations induced by vomiting, and occurring around the circumference at the cardioesophageal junction. It is presumably due to pressure changes in the stomach and esophagus during vomiting and the continuous regurgitation of acid gastric juice over the cardia. The ulcers so found are superficial with a vertical axis, from 0.5 to 3 cm. long and up to 0.7 cm. wide. They involve the distal

esophagus and proximal cardia and are at right angles to the gastroesophageal junction. They are multiple and a few may occur in the cardia only, but not vice versa. Copious amounts of blood are found in the gastrointestinal tract, and, microscopically, the ulcers penetrate through the mucous membrane and are based on, and limited by, the submucosa or muscularis mucosae. These layers are infiltrated by red blood cells and leukocytes. Graham *et al.*[26] say that the initial lesion is a laceration of the mucosa, which becomes inflamed from the gastric juice, leading to ulceration. Histologically, the findings are essentially the same as those found at the tear of a spontaneous rupture of the esophagus.

The mediastinum commonly reveals widespread necrosis and gangrene of the tissues. This is associated with intense inflammation of the pleura and pulmonary collapse. A vast area may be infected and this necrotic mediastinitis is, in fact, the worst menace to life. If a patient is seen after 24 hours have elapsed following the rupture, then the prognosis is very poor. Most of the escaped material enters the mediastinum and is bounded laterally by the right and left mediastinal pleura, anteriorly by the heart and posteriorly by the vertebrae. It may be prevented from spreading upwards by the hili.

One of the most common findings, occurring in about 85 per cent of cases, is a hydro- or pyo-pneumothorax, which can contain up to a gallon of fluid, and its appearance depends on whether the mediastinal pleura ruptures immediately, or remains intact. In the former case, a hydropneumothorax follows with little or no mediastinal emphysema, whereas, if the pleura resists rupture, even for a short time, mediastinal and cervical emphysema will be a prominent feature with little or no pleural fluid. Rupture of the pleura is said to take place in 77 per cent of cases and, when it does, hydropneumothorax is twice as common on the left as on the right, which follows the greater frequency of tears on this side.

A pleural effusion is probably slightly more common than a hydropneumothorax, its incidence being estimated at 90 per cent. It is bilateral in 7 per cent of cases. The effusion may occur without rupture of the parietal pleura and, in this case, it is probbably a transudate from the effect of hydrochloric acid or food debris on the pleura. Similarly, an effusion may arise in the contralateral pleural cavity or in the pericardium. Empyemata, often loculated, may follow the effusion or hydropneumothorax, and basal collapse with superimposed pneumonia, which is slow in resolving in patients who recover, is a not unusual feature. Tension pneumothorax is a rare sequel to spontaneous rupture of the esophagus.

CLINICAL FINDINGS

Most of the reported series show a higher incidence of spontaneous rupture of the esophagus in males. Anderson[4] states that 86 per cent are male, although others do not give so high a figure. The condition is rare under 35 years and the commonest age for it to occur is between 50 to 60 years. The youngest reported case occurred in a child of 2 years and the oldest in a man of 75 years. The 4 cases reported here were all males, their ages respectively being 59 years, 56 years, 37 years and 81 years.

The classic history is that of a healthy, robust male, a heavy eater, and fond of alcohol, who vomits following a large meal. The vomiting gives rise to a sudden, severe pain in the epigastrium and left lower chest which is rapidly accompanied by shock, dyspnea and cyanosis. The pain gets progressively worse and is not relieved by morphine. On examination, the patient is weak, pale and sweating, and possibly cyanosed, with rapid labored respirations, a low blood pressure and a fast, feeble pulse. The upper abdomen is rigid but the lower abdomen is not and there is no real tenderness.

Pain and vomiting are equally common but the pain is a striking feature. The vomiting tends to cease as the pain develops. Pain is felt in the epigastrium and left

lower chest but is often referred to the back in the region of T 10, to the substernal area, and to the left shoulder. It is worse sitting and it is often mistaken for the pain of a perforated peptic ulcer, although the site is higher. Dysphagia is not common and ingestion of fluids has been reported to cause no pain on swallowing but has increased the severity of the chest pain. A single small hematemesis is not infrequent.

Chest signs are prominent and commonly consist of hydropneumothorax, effusion, empyema, pneumothorax, collapse and pneumonia, although in a small number of cases (9 per cent, according to Hochberg and Parlamis[28]) the chest may be clear. Clinically, crepitations at the left base are rapidly followed by dullness on percussion and absent breath sounds. The pain is made worse by breathing, and with the development of these chest complications, the patient becomes extremely ill with rapid, labored respirations, and lies flat or on one side, immobile, often with his knees drawn up and keeping his abdomen still, being very unwilling to move. The dyspnea and cyanosis depend on the severity of the pain, the presence or absence of an effusion or surgical emphysema, as well as on the existence of a tension pneumothorax.

Surgical emphysema is found in approximately 60 per cent of cases and can occur as soon as 1 hour afterwards, but subdiaphragmatic air has never been reported. Air may be visible in the neck or mediastinum and is probably best seen on the posteroanterior chest roentgenogram where, when mediastinal, it is often localized to the left of the aortic arch or descending thoracic aorta. From here, it rapidly becomes generalized and spreads to the neck and face. The localized mediastinal emphysema often occurs prior to the appearance of any physical signs and may precede the appearance of subcutaneous emphysema by 1 hour or more. It is a most important sign in the diagnosis and, thus, a chest roentgenogram is probably the most important investigation. A repeat study should be done if there is still clinical doubt, as occasionally there is some delay in the appearance of the air.

Following rupture, food debris and gastric contents collect in the mediastinum and are prevented from spreading upwards by the hili. This does not apply to air and crepitations may be audible at the hili. A cardiac systolic crunch (Hamman's sign) can occasionally be heard. An overpenetrated chest roentgenogram will usually reveal this mediastinal collection as a fusiform opacity with a fluid level through the shadow of the widened mediastinum and may cause displacement of the heart and mediastinum to the opposite side. Almost inevitably it will give rise to sepsis, which increases the shock. The patient becomes pale, anxious and weak, is restless and sweating. The temperature rises to 99° or 100°F. and the hypotension, which is present at the onset, gets rapidly worse in 70 per cent of cases. The degree of shock depends on the severity of the pain, the extent of the blood loss and hypoxia and the increased mediastinal tension. This increased tension may also cause compression and retardation of the venous return, a superior mediastinal syndrome resulting. The patient complains of severe thirst and movements of the spine make the pain worse, and eventually neck rigidity appears, if the retropharyngeal space becomes involved. The voice may be altered by the same mechanism, becoming high-pitched and hoarse, but a nasal twang is more common. If no treatment is undertaken, death follows rapidly.

Most observers report upper abdominal rigidity and not lower, but the finding of abdominal tenderness is not definite. Case histories vary from recordings of exquisite tenderness to no tenderness at all, but the incidence of exquisite tenderness is extremely rare and the significant point appears to be the discrepancy between the pain and tenderness.

REPORT OF CASES

CASE 1. Male, aged 59 years, with a history of

intermittent indigestion for many years and exacerbation for a week. On the day prior to admission, he complained of continuous epigastric pain and vomited several times. At 7:00 A.M. on the morning of admission (February 24, 1960), he had a sudden bout of severe vomiting of brownish fluid, which brought on very severe pain. This was located in the epigastrium and in the back and later spread all over the abdomen. It was persistent. There was no dyspnea or chest pain.

On examination, the patient was flushed and perspiring and obviously in severe pain. He was apyrexial, with a pulse of 140 and a blood pressure of 150/100. Abdominal rigidity and tenderness were present and there were no bowel sounds. Respirations were normal and rectal examination revealed no abnormality. A diagnosis of a perforated peptic ulcer was made.

Roentgen Findings. Erect and supine roentgenograms of the abdomen were taken. There was no subdiaphragmatic gas, but on the supine study air was noted alongside the lateral wall of the descending thoracic aorta (Fig. 1). The chest roentgenogram showed mediastinal emphysema near the aortic knuckle and there was

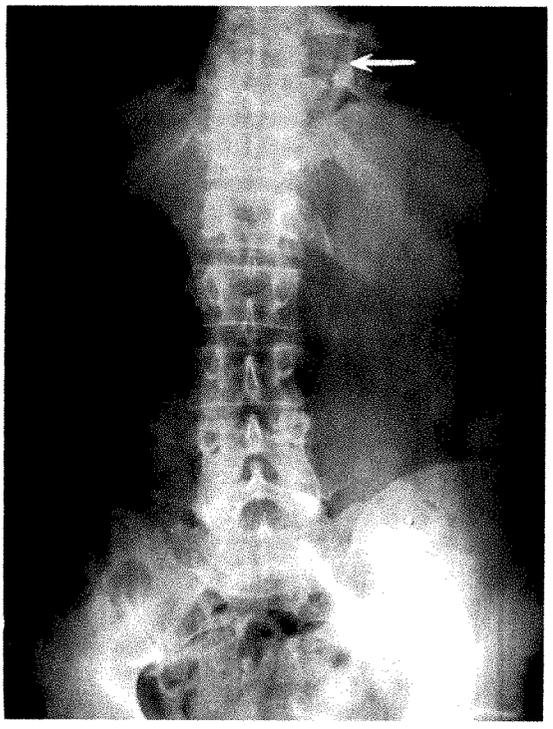


Fig. 1. Case 1. Supine roentgenogram of the abdomen. A linear gas shadow can be seen along the descending thoracic aorta.

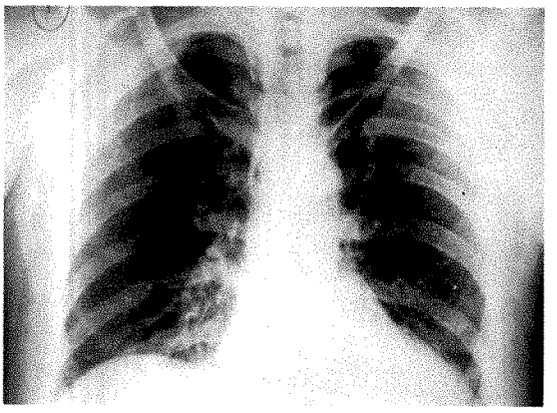


Fig. 2. Case 1. A fine linear gas shadow is present near the aortic knuckle and some pleural reaction can be seen in the left costophrenic angle.

a small left pleural effusion (Fig. 2). The diagnosis was spontaneous rupture of the esophagus, or rupture of a diverticulum in the large intestine with retroperitoneal and intrathoracic spread of gas.

Three hours later, surgical emphysema was present in the neck (Fig. 3). The diagnosis of rupture of the esophagus was now considered most probable, but, nevertheless, a laparotomy was performed as it was felt that an intra-abdominal catastrophe could not definitely be excluded. At operation, there was a chronic duodenal ulcer but no evidence of perforation.

Conservative treatment was adopted, which included antibiotics, gastric aspiration, blood pressure readings every 15 minutes, intravenous fluids and nothing by mouth. Over the next few weeks the patient continued to hold his own but the lesion at the left base deteriorated. Collapse and consolidation followed the effusion, which itself increased in extent (Fig. 4), and these changes were slow to resolve despite antibiotics and physiotherapy. In fact, the chest roentgenogram was not clear until March 18, 1960. A lipiodol swallow study on March 2, 1960 revealed no abnormality. Oral feeding was recommenced on March 4, 1960. The patient was regularly followed up in out-patient clinic and when last seen on November 12, 1962 had no complaints.

Case II. Male, aged 56 years. This was an emergency admission on October 16, 1951, because of severe epigastric pain and vomiting for 7 hours previously. There had been no previous abdominal complaints. The vomiting coincided with the onset of the pain, which came on while

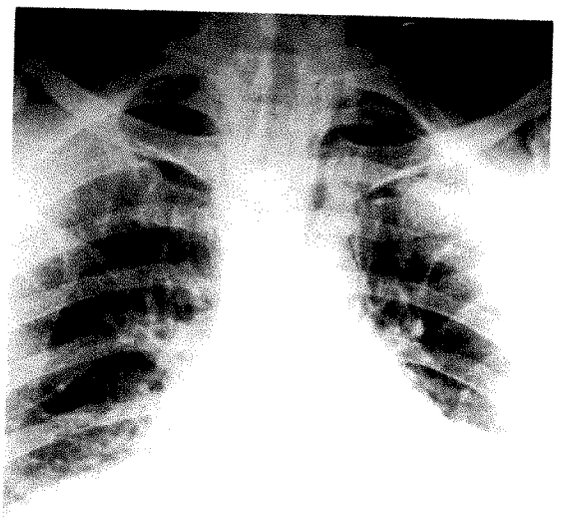


FIG. 3. Case 1. Chest roentgenogram made 3 hours after Figure 2 showing well-marked cervical surgical emphysema, mediastinal emphysema and an effusion with some consolidation developing at the left base.

walking, and the pain had since then increased in severity and was worse on movement. It was maximal in the epigastrium and also radiated posteriorly and upwards to the midscapular region. The vomiting later became continuous. There was a past history of chronic bronchitis with acute exacerbations and he admitted to an intake of 20 pints of beer daily.

On examination, the patient was in severe pain and was unwilling to lie down. There was marked tenderness in the right hypochondrium and epigastrium with guarding and local rigidity, but elsewhere the abdomen was slack. The blood pressure was 130/80, pulse 100. The diagnosis was a perforated duodenal ulcer. Conservative treatment was decided upon and, because of the localized signs, intravenous fluids and antibiotics were administered. A Ryle's tube was passed and a small quantity of bright red blood was found in the aspirate. Soon afterwards the patient had a rigor and a small hematemesis. His blood pressure was then 95/65, pulse 160.

Roentgen Findings. On the following day (October 17, 1951) a chest roentgenogram showed that surgical emphysema was present in the neck and alongside the aortic arch (Fig. 5). A more penetrated, localized roentgenogram showed an air-fluid level through the heart shadow and also the "V" sign, *i.e.*, air linearly along the left side of the descending thoracic aorta and outlining the left diaphragmatic surface (Fig. 6). A left pleural effusion was evident and air was also present along the diaphragm

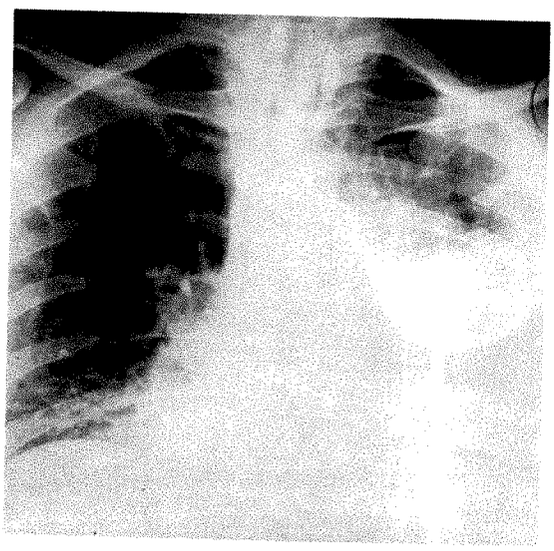


FIG. 4. Case 1. Roentgenogram made 5 days later. There has been marked deterioration in the appearances at the left base.

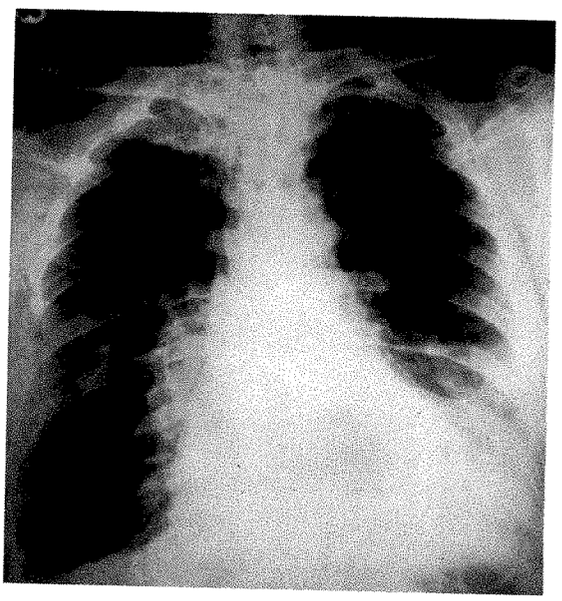


FIG. 5. Case II. Chest roentgenogram on the day following admission. Cervical surgical emphysema is present and mediastinal emphysema is seen near the aortic knuckle. A left pleural effusion is present.

behind the heart. The possibility of rupture of the esophagus was then considered.

Next day, the patient was much improved and bowel sounds were present. The left effusion had increased slightly and the cervical surgical emphysema was still present. He continued to improve gradually. A barium swallow study was done on October 30, 1951 and this showed a periesophageal cavity (Fig. 7 and 8). Esophagoscopy on November 7, 1951 showed slight narrowing at 31 cm. but the mucosa appeared normal.

He was discharged on November 22, 1951 and a repeat barium swallow examination on May 10, 1952 and again in 1957 showed no abnormality.

Case III. Male, aged 37 years. The patient, a healthy robust male, was admitted on January 17, 1963 at 12:30 P.M. complaining of severe pain in the abdomen, lower chest and in the region of the lower thoracic vertebrae. On the evening before, he had had a large meal and immediately afterwards had felt sick and vomited. He had no pain prior to feeling ill, but immediately after he vomited he developed severe pain in the abdomen which he described as tearing in nature, "as though muscles had torn." He had had pain in the lower chest and back for 15 hours on admission. The vomiting had ceased and there was no nausea, but despite an injection of morphine, the pain persisted only slightly diminished in intensity. He also complained of severe thirst.



Fig. 6. Case II. An example of the "V" sign. Linear gas is present along the descending thoracic aorta and along the left diaphragmatic surface. Gas is also visible along the diaphragm behind the heart shadow and an air fluid level can be seen through the heart outline. (Reproduced with permission of *Proc. Roy. Soc. Med.*, 1965, *58*, 857.)



Fig. 7. Case II. Anteroposterior barium swallow study showing the periesophageal cavity (arrow marks the site of the tear).

Examination revealed a man in considerable pain and looking hot. His respirations were shallow with bilateral basal crepitations but the percussion note was clear. There was slight dyspnea and cyanosis. The temperature was 101°F. The abdomen was tender in all areas but particularly in the epigastrium and there was some guarding but no diminished movement. The diagnosis rested between a preforated peptic ulcer, an aortic dissection, acute pancreatitis or rupture of the esophagus.

Roentgen Findings. Erect and supine roentgenograms of the abdomen were viewed at 4:00 P.M. Linear air was seen through the heart shadow with some mottled areas lying medially (Fig. 9). These latter were interpreted as probably due to extruded food particles. There was no subdiaphragmatic air. A chest roentgenogram was then taken (Fig. 10) and an air-fluid level was noted overlying the aortic knuckle. A left pleural effusion appeared to extend as a mediastinal effusion to the level of the aortic arch superiorly. There was no cervical subcutaneous emphysema. A lipiodol swallow study was then undertaken and showed no

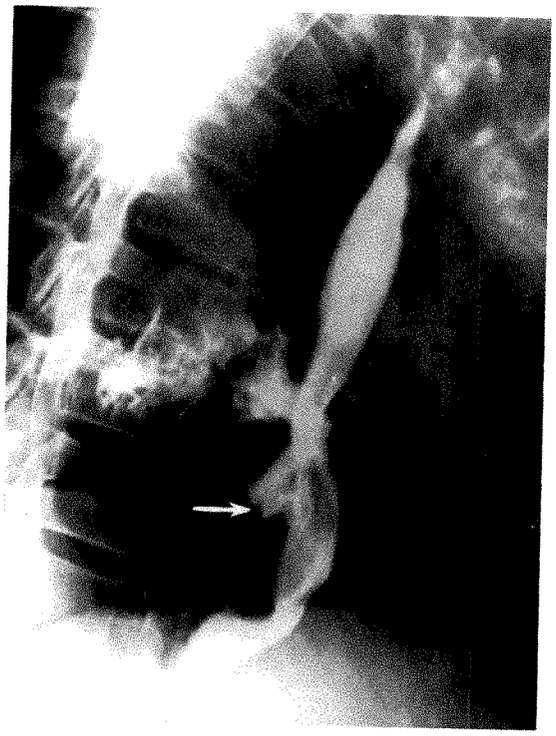


FIG. 8. Case II. Lateral barium swallow study showing the periesophageal cavity (arrow marks the site of the tear).

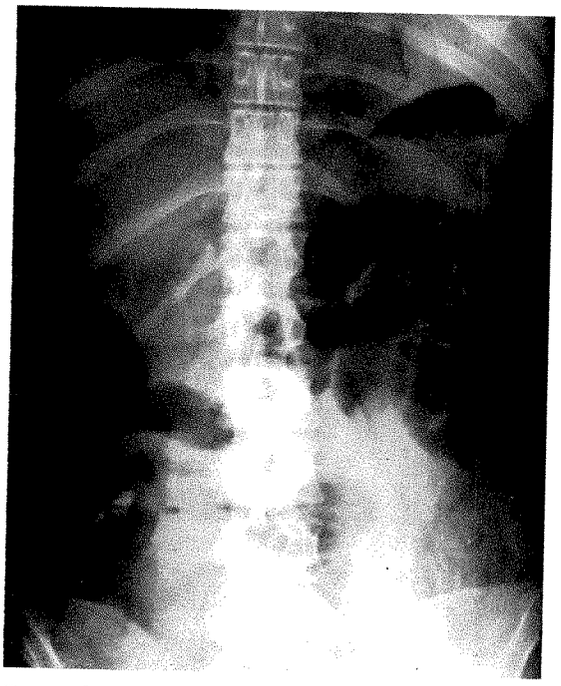


FIG. 9. Case III. Erect roentgenogram of abdomen on the day of admission. A translucent line can be seen through the heart shadow with mottled shadows, representing food particles, lying medially. No subdiaphragmatic air.

extravasation. Nevertheless, a diagnosis of spontaneous rupture of the esophagus was made.

At 10:00 P.M. a left thoracotomy was done through the 9th rib. Free fluid was present in the pleural cavity. A small hole was found in the mediastinal pleura over the esophagus, from which a bolus of food projected. The pleura was incised and a large collection, among which were recognizable food debris, was revealed. This was cleared and a longitudinal tear in the esophagus, approximately $\frac{1}{2}$ inch long, was sutured with catgut and an intercostal drain was left in.

Postoperatively, the patient developed partial collapse, consolidation and an empyema at the left base. This was drained on February 11, 1963. It healed well. On April 3, 1963 he was discharged with a completely clear chest, on a full diet and no follow-up was deemed necessary.

CASE IV. Male, aged 81 years. The patient had an attack of nausea with forceful vomiting on the afternoon prior to admission (May 1, 1963). Following this, he complained of severe upper abdominal pain which lasted for 4 to 5 hours and then subsided. Later that night in bed, the pain returned and was now more severe and radiated across the abdomen and into the back. It was accompanied by copious vomiting, which did not relieve the pain. The pain persisted from then on.

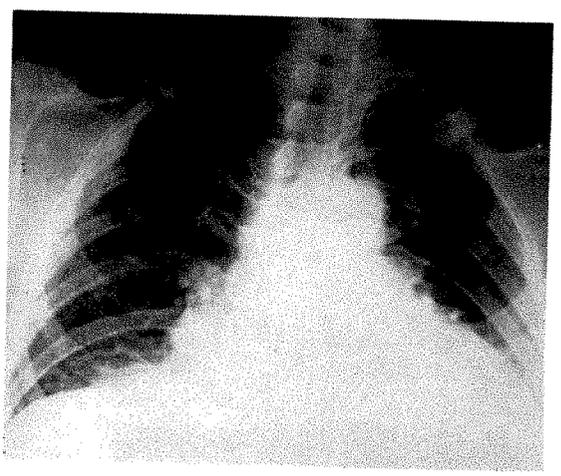


FIG. 10. Case III. Chest roentgenogram showing a left effusion extending alongside the mediastinum to the aortic arch. An air-fluid level could be seen overlying the aortic knuckle on the original study but could not be reproduced satisfactorily. No surgical emphysema.

He had a prostatectomy in late 1962 and complained of occasional slight cough with sputum. There was no other relevant past history.

On examination, the patient was in great pain but not shocked. His blood pressure was 145/85; pulse regular with good volume. The chest was clear. The abdomen was tense but not rigid and was tender on palpation in the left hypochondrium. Bowel sounds were present. There was a right lower paramedian scar. A diagnosis of an exacerbation or perforation of a peptic ulcer, or acute pancreatitis was considered. However, a serum amylase estimation was less than 200 units. Aspiration of the stomach was started and intravenous fluids and $\frac{1}{3}$ gr. omnopon were given. The patient improved on this regimen and the fluids and aspiration were stopped next day (May 2, 1963).

Roentgen Findings. Erect and supine abdomen roentgenograms were made on May 2, 1963 and showed no evidence of acute intestinal obstruction or perforation. However, a left effusion was noted with some mottled gas shadows alongside the lower thoracic aorta (Fig. 11). The possibility of spontaneous rupture of the esophagus was immediately raised and chest roentgenograms and a barium swallow study were arranged. The chest roentgenogram (Fig. 12) showed an increase in the left effusion which now also appeared to extend along the mediastinal surface behind the heart shadow. There was no subcutaneous emphysema. A barium swallow study (Fig. 13, *A* and *B*) revealed no extravasation but did show a small, constant niche on the left lower aspect of

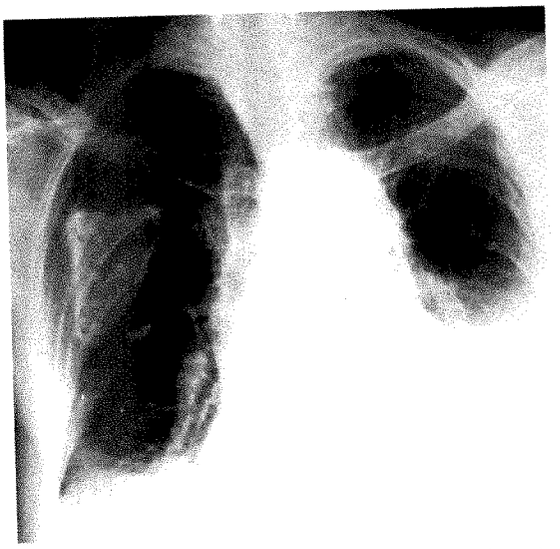


Fig. 12. Case IV. Chest roentgenogram showing the effusion extending along the mediastinal surface.

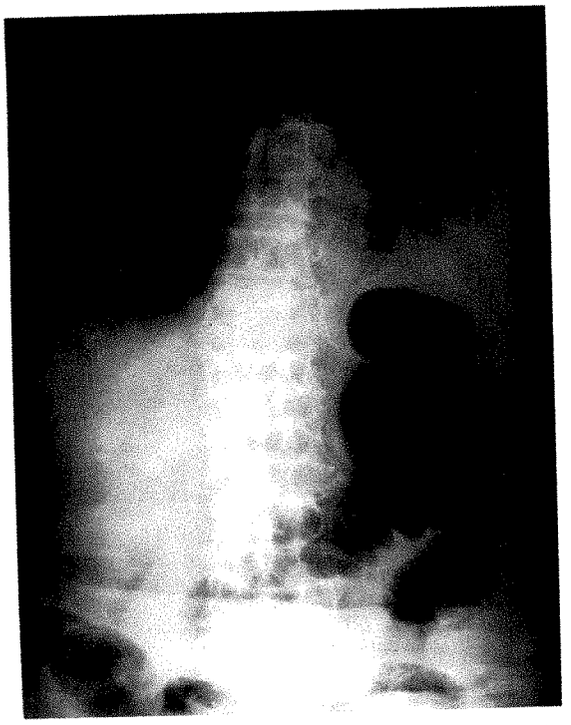


Fig. 11. Case IV. Erect roentgenogram of the abdomen showing mottled shadows alongside the lower thoracic aorta with a left pleural effusion.

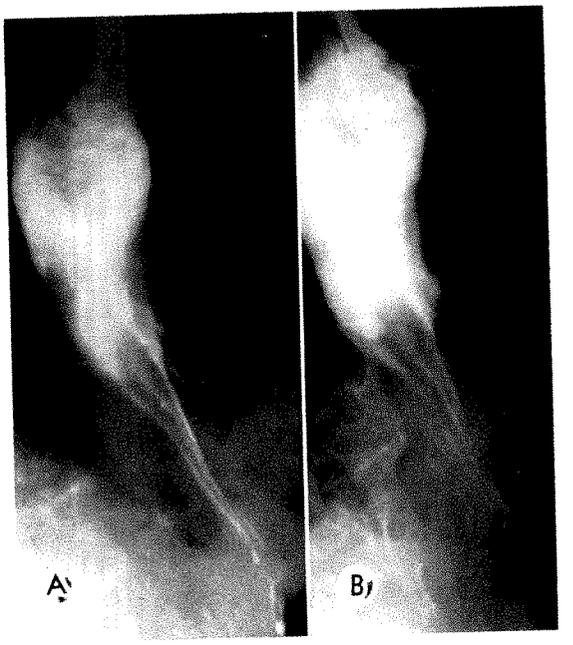


Fig. 13. Case IV. (*A* and *B*) A barium swallow study showing a small constant niche in the lower esophageal wall.

the esophagus, adjacent to the mottled lung shadows previously mentioned. These shadows were regarded as being food residue in the mediastinum, with subsequent sealing of the rupture.

The left effusion was tapped and over 500 ml. of fluid, containing bile and pus, was aspirated. The patient was transferred to the thoracic unit of May 4, 1963.

As the rupture had then been present for 4 days and the patient was too weak for surgical repair, intercostal drainage was instituted. A further chest roentgenogram on the following day showed fluid posteriorly and a second tube was inserted and 600 ml. more fluid was aspirated. The patient's general condition deteriorated rapidly after this, and he died on the same day (May 6, 1963).

At postmortem examination, a rupture of the esophagus was found with a mediastinitis and a left-sided empyema. In addition, the patient was found to have a strangulated left inguinal hernia.

DIAGNOSIS

CLINICAL

Spontaneous rupture of the esophagus is not often diagnosed preoperatively or premortem but this is probably because it is not considered in the differential diagnosis and indeed, Hochberg and Parlamis[28] maintain that the frequency of its diagnosis is in direct relation to the index of suspicion. The first correct clinical diagnosis is attributed to Meyer[37] in 1858. Nowadays, approximately 25 per cent are diagnosed correctly, most commonly being misdiagnosed as perforated peptic ulcers.

The diagnosis can be easy, and Wangensteen[49] once made it over the telephone. In fact, most cases tend to follow the classic description rather closely. A diagnostic triad of vomiting, pain in the chest and epigastrium, and subcutaneous emphysema justifies a thoracotomy, according to Mackler,[33] and he makes the point that a left thoracotomy should be done, even if there is a right-sided effusion, since, even in this instance, the tear is still more commonly on the left. Barrett[6] maintains that a combination of rapid respirations, abdominal rigidity and subcutaneous emphysema is diagnostic, especially if these changes are precipitated by vomiting or retching. Other features which may indicate the diagnosis are the amount of shock and the chest signs.

Many authors contend that surgical emphysema is almost diagnostic and Ridgway and Duncan,[41] for example, found that it occurred in 17 out of their 27 cases, and Ware *et al.*[50] found it in 50 out of 70 cases. However, other conditions may, although admittedly very rarely, also give rise to surgical emphysema and among those quoted are perforated peptic ulcer, rupture of the uterus and following a tonsillectomy or dental extraction. Again, if the mediastinal pleura is ruptured almost immediately, a hydropneumothorax will follow but subcutaneous emphysema is unlikely, whereas, if the pleura resists rupture, even for a short time, subcutaneous emphysema rapidly follows. Naclerio[39] maintains that the optimum time for operation is when mediastinal or cervical emphysema is present without any pleural reaction, as it indicates that the pleura is still intact.

ROENTGENOLOGIC

The most important single investigation is an erect chest roentgenogram. This will immediately exclude subdiaphragmatic air or a spontaneous pneumothorax. It may also reveal mediastinal or cervical emphysema, and possibly the "V" sign or the presence of an effusion or hydropneumothorax. Surgical emphysema is often initially localized near the aortic knuckle or along the descending thoracic aorta and is the most significant and practically diagnostic finding. One note of caution, however—the time of appearances of the air may, on occasion, be late and in cases of clinical doubt, repeat chest roentgenography should be considered.

The "V" sign (Fig. 6), regarded by Naclerio[39] as being pathognomonic, is due to air spreading linearly in the fascial planes of the mediastinal and diaphragmatic pleura in the region of the lower esophagus,

thus forming a V in the left hemithorax on the posteroanterior chest roentgenogram.

A penetrated posteroanterior chest roentgenogram may show a fusiform opacity of extruded gastric contents through the heart shadow, possibly with a fluid level. A mottled appearance within this opacity means food particles and this was noted and proven in 2 of our cases (Cases III and IV).

A lipiodol swallow study will usually confirm the presence of an esophageal leak but this can also fail. It failed in Case III of ours, because the actual tear was closed off by a large food particle, firmly wedged in position.

FUTHER INVESTIGATIONS

Other methods of diagnosis include aspiration of fluid from the pleural cavity, which may confirm the diagnosis, if acid or food debris are discovered. When blood is mixed with gastric juice, the aspirate is occasionally not recognizable as such, being dirty brown in color and having a sour odor, due to digestion of the blood by the juice. This differentiates it from a spontaneous hemothorax when blood would also be found, but, in this case, whole blood. Methylene blue can be given orally prior to aspiration and is confirmatory if recovered and removes the necessity to have the patient moved and roentgenographed, but this procedure can fail if there is a periesophageal pocket, or if the tear is sealed off. This was so in the case of Naclerio.[39] Recovery of the dye indicates that rupture of the pleura has occurred and it is, therefore, late and the patient is extremely ill. If possible, the diagnosis should be confirmed by lipiodol swallow study or esophagoscopy.

DIFFERENTIAL DIAGNOSIS

It is estimated that about 25 per cent of patients with spontaneous rupture of the esophagus undergo unnecessary laparotomy. The diagnosis must be differentiated from the following conditions:

1. Perforated peptic ulcer. This is the commonest misdiagnosis. A previous ulcer history with free subdiaphragmatic air on the erect abdomen roentgenogram suggests this far more common condition, as does the absence of dyspnea and cyanosis. Subcutaneous emphysema and a pleural effusion are very rare complications of a perforation and the presence of these signs would help exclude it.

2. Spontaneous pneumothorax may simulate all the symptoms and signs of spontaneous rupture of the esophagus, but the pain is not usually so severe and the prostration not so marked. There is no vomiting, very rarely subcutaneous emphysema, and fluid at the base does not usually appear until 24 to 28 hours later. A chest roentgenogram is diagnostic.

3. Coronary thrombosis. This is often difficult to differentiate because of the severe chest pain in both conditions, but the absence of a previous cardiac history and the electrocardiographic changes usually are decisive. Also the presence of subcutaneous emphysema or pleural effusion will exclude a coronary lesion.

4. Bronchopulmonary fistula. Both conditions can present with subcutaneous and mediastinal emphysema, pain and collapse of a portion of the lung, dyspnea, shock and prostration. A fistula, however, causes marked coughing with sputum and very little vomiting, and aspiration of a pleural effusion in spontaneous rupture of the esophagus may reveal gastric contents or hydrochloric acid.

5. Acute pancreatitis. The acute pain in the back and upper abdomen, the cyanosis and the abdominal rigidity and tenderness are more severe with pancreatitis. The serum amylase may be raised. There is no subcutaneous emphysema and the history, chest symptoms and signs, and roentgenographic appearance should decide.

6. Acute cholecystitis. The history should be of value and the presence of a gallstone on a roentgenogram will give an indication. There is no subcutaneous emphysema.

7. Dissecting aneurysm. The pain in both conditions is excruciating, but tends

to wane after reaching a climax with dissection, whereas it gets progressively worse with rupture.

8. Rupture of a hiatus hernia may, of course, reproduce the symptoms and signs of spontaneous rupture of the esophagus in every way, but the treatment of both conditions is exactly the same and the differentiation is, therefore, not of great importance.

The above are the main disease entities likely to be confused with spontaneous rupture of the esophagus, but an exhaustive list would include such less likely differentiations from mesenteric thrombosis, intestinal obstruction, volvulus, pulmonary embolism or infarction, mediastinal emphysema and pulmonary interstitial emphysema from rupture of an emphysematous bulla, splenic infarction, rupture of the gallbladder, strangulation of the bowel, rupture of a subphrenic or hepatic abscess and fulminating staphylococcal infections of the kidney.

TREATMENT

In 1900, Bowles and Turner[10] were the first to recommend mediastinotomy and suture and this method of treatment was also advocated by Walker in 1914.[48] In 1948 Jackson and Jackson[29] suggested rib resection and gastrostomy. The first successful operative cure is attributed to Sencert in 1911.[43] Graham,[25] who drained empyemata resulting from spontaneous rupture of the esophagus, had 2 patients who subsequently recovered but both had a high morbidity, as they later developed fistulae.

Collis, Humphreys and Bond[14] attempted transthoracic repair with direct suture but the patient died within 24 hours postoperatively. A further 2 cases of theirs recovered with simple thoracotomy, drainage and gastric suction. Foggitt[22] also attempted direct repair of the tear, using an intra-abdominal approach, but this also was unsuccessful. Then, Barrett[7] reported a successful suture, using the transthoracic approach, combined with drainage of the pleural cavity.

Accurate diagnosis is essential for successful treatment, and Ware *et al.*[50] state that any measure taken to drain the mediastinum helps. The best treatment is immediate thoracotomy and repair, with supportive therapy preoperatively. Shock should not delay operation. In one series,[32] there was a 75 per cent survival rate by simple drainage, although a high morbidity was recorded. Hypotension was not considered a contraindication to operation.

The essentials of therapy are:

1. Immediate treatment of shock with transfusion of blood, plasma and electrolytes.

2. If a tension pneumothorax is present, this is relieved instantaneously by needle aspiration of the pleura with intercostal catheter and continuous suction and underwater seal.

3. Intravenous chemotherapy is instituted until the temperature drops to normal levels for 48 hours.

4. Operation is then undertaken and the operation of choice is a left thoracotomy with direct suture of the tear. When the pleural cavity is opened, it is drained and all food particles are meticulously removed. The mediastinal pleura, which is usually bulging, is then incised in its entire length in order to decompress the mediastinum. This usually leads to a rapid improvement in the patient's general condition. A thorough debridement is then carried out and the mediastinum is drained. Lastly, the esophagus is exposed and sutured. The suturing is interrupted and a flap of mediastinal pleura to overlap the suture line is included. Subsequently, free drainage of the mediastinal pocket is maintained through the pleura to the outside and many surgeons irrigate with saline. Local antibiotics may be included in the solution. The optimum time to operate is considered to be prior to rupture of the pleura and Gardner[23] and Samson[42] report 2 such cases which had a subsequent rapid convalescence.

5. Nothing is given by mouth for approximately 10 days postoperatively, a

Ryle's tube being left in the stomach with continuous suction. This prevents distention of the stomach with resulting pressure on the suture line.

6. To increase the respiratory reserve, the contralateral side is aspirated if an effusion is present here and bronchoscopy may be performed to re-expand any collapsed areas of lung.

7. Later, during convalescence, barium swallow study and esophagoscopy should be carried out, and if a stricture should be found at the site of the tear, dilatation can be performed. At the same examination, a barium meal study will reveal any associated gastric or duodenal lesions.

If direct suture of the tear proves impossible, the best alternative appears to be drainage of the pleural cavity with underwater seal, without suture of the tear. Many surgeons report successes with this technique, but a careful survey of the records by Mackler[33] revealed probably 6 true cases of spontaneous rupture treated in this manner, 2 of which recovered. This would indicate a mortality rate of 66 per cent but other sources quote lower figures. Mediastinotomy is often done at the same time, either superiorly or posteriorly and, occasionally, the mediastinum has been drained via the abdomen. With either of these two techniques, a mediastinal abscess invariably follows and complications like empyemata and mediastinitis commonly occur. Other surgical techniques include rib resection, delayed esophageal closure and segmental esophageal resection. Five cases treated by rib resection alone have been recorded by Ware *et al.*,[50] but the same authors recommend thoracotomy and repair as the treatment of choice. Delayed esophageal closure is not recommended and probably leads most frequently to complications and is more likely to disrupt. One case only of segmental esophageal resection has been tabulated,[35] and the patient died postoperatively.

Conservative treatment is not usually advocated unless the patient has already survived 48 hours when first seen, or unless the patient's condition is extremely poor. If it is decided to treat a patient in this manner, vigorous supportive therapy is called for: shock is combated; fluid is aspirated from the pleural cavity, and, if a tension pneumothorax is present, this is relieved using negative pressure to expand the lung; antibiotics and sedatives are administered or an intercostal block is done to relieve the pain. The patient is intubated and should subcutaneous emphysema prove embarrassing, this can be released by an incision made above the suprasternal notch with a catheter left *in situ*. In any of the approaches referred to, except the method of direct repair, complications, which include abscess formation, mediastinitis and empyema, are common.

Of the 4 new cases reported here, 1 was treated by thoracotomy and direct suture, one was drained, but the other 2 were treated conservatively. Three are now alive and well. Of the 2 treated conservatively, 1 (Case I) had no complaints 2½ years later, and the other (Case II) 6 years later. The third patient (Case III) was discharged without follow-up almost 3 months postoperatively. In retrospect, one of the reasons why the first case, which was treated conservatively, did so well, may be because he differed from the usual classic case in that his rupture occurred at 7 A.M. and did not follow a heavy meal. The absence of food debris in his mediastinum may have been a big factor in his eventual recovery.

PROGNOSIS

In general, the prognosis is poor and depends on such factors as the size of the tear, the rapidity with which the diagnosis is made and the adequacy of treatment. Although 2 of our 4 patients recovered on conservative treatment, the best results appear to follow urgent, aggressive surgery. Shock must be combated vigorously but should not unduly delay operation and blood and antibiotics are administered immediately.

The over-all mortality rate when the condition is untreated, estimated as re-

cently as 1961, is considered to be 25 per cent at 12 hours and 70 per cent at 24 hours.[32] Up to 1946, according to Eliason and Welty,[20] the mortality rate was almost 100 per cent, except for the 2 cases of Graham,[25] who survived. In 1947, Barrett[7] treated a case successfully by direct repair and several cases were subsequently also successfully treated in the same way, but no case had survived without surgery.[3,32]

Thoracotomy and suture of the tear, which is now the recommended method of treatment, have a mortality rate of from 10 to 33 per cent according to different observers, with a low morbidity, averaging from 13 to 22 days, whereas, in the alternative treatment of choice, surgical drainage without suture of the tear, the mortality rate varies from 47 to 66 per cent with a morbidity rate from 6 weeks to 1½ years. Samson[42] compared two series of 15 patients treated by these two procedures and found that 10 had survived thoracotomy and direct repair, while 8 survived with drainage only, but the morbidity and postoperative complications were far greater in the latter group.

One case of segmental esophageal resection is on record; the patient did not survive. A 100 per cent mortality rate has been quoted for the conservative approach. Yet, 2 of our cases treated in this way survived and there may be many other such cases which have not been reported. Survival here probably depends on the immediate adoption of full supportive therapy, as already indicated. When conservative treatment is undertaken, death commonly follows from shock and tension pneumothorax in the early stages and from mediastinal and pleural sepsis later.

SUMMARY

Four new cases of "spontaneous" rupture of the esophagus are reported, 3 of which recovered completely, 2 with conservative treatment and 1 following direct suture of the tear.

The importance of early diagnosis with prompt and aggressive treatment, either by full supportive therapy alone or, preferably combined with surgery, is emphasized.

The premier part that radiology plays in making such an urgent diagnosis is stressed and is fully discussed.

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THE ESOPHAGOBRONCHIAL FISTULA*

CASE REPORT AND REVIEW OF THE LITERATURE

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ESOPHAGOBRONCHIAL fistulas present a difficult problem of prompt and accurate diagnosis. The diagnosis offers the patient a potential cure from repeated pulmonary infections and symptoms of bronchitis and bronchiectasis. The radiologist usually plays the key role in demonstrating the fistulous tract. On the one hand, the esophagobronchial fistula is uncommon enough so that it is not often in the forefront of the differential diagnoses, and, on the other hand, the fistula is usually difficult to demonstrate.[1] Most patients have histories of recurrent episodes of pneumonitis, cough, or production of purulent sputum.[8,12] A most characteristic symptom is a paroxysmal cough, particularly following the ingestion of liquids.[1] However, this symptom complex may not be present in a small and inconstant fistula. Basilar rales, malodorous breath, and a chronically ill patient may also be noted; however, many patients maintain surprisingly good health.[3,10]

Esophagobronchial fistulas are divided into 2 broad categories—acquired and congenital. Although this discussion shall be limited to the esophagobronchial fistula, the tracheoesophageal fistula presents the same type of clinical symptomatology. In contrast to fistulas associated with esophageal atresia,[7] the presentation of respiratory esophageal fistula without esophageal atresia is less dramatic and symptomatology may be delayed until adult life.[9] Since the discussion of tracheal esophageal fistula is well covered in the radiologic literature, this communication will concern only those cases without associated esophageal atresia or stenosis and with the esophageal respiratory fistula below the carina—the esophagobronchial fistula. Recently, we encountered a case of esophagobronchial fistula via an esophageal diverticulum communicating with an azygos lobe.

REPORT OF A CASE

Mrs. V. L. is a 39 year old Negro female who had a normal infancy and childhood. At age 30 she developed a pulmonary abscess in the superior segment of the right lower lobe (Fig. 1*B*). The earliest available chest roentgenogram, taken 4 months previous to the development of the abscess, demonstrated an azygos lobe somewhat denser than normal (Fig. 1*A*). She was hospitalized at Letterman General Hospital for treatment of this abscess. Sputum examinations and culture revealed no evidence of tuberculosis or other fungal disease, but the patient did have a positive tuberculin skin reaction. A specific bacterial agent was not identified other than "normal flora" from sputum cultures. After a lengthy hospitalization, she was discharged with complete resolution of the abscess and surrounding infiltration.

The patient was asymptomatic for 7 years following cure of the lung abscess until the age of 37 years, when she developed a chronic cough, and began to experience difficulty sleeping because of "choking and gagging," made especially worse by lying on her right side. Her symptoms became progressively worse over the next 2 years with no relief on various regimens of medication prescribed in the outpatient department.

In August of 1965, because of this chronic, unresponsive cough, bronchoscopy and bron-

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This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

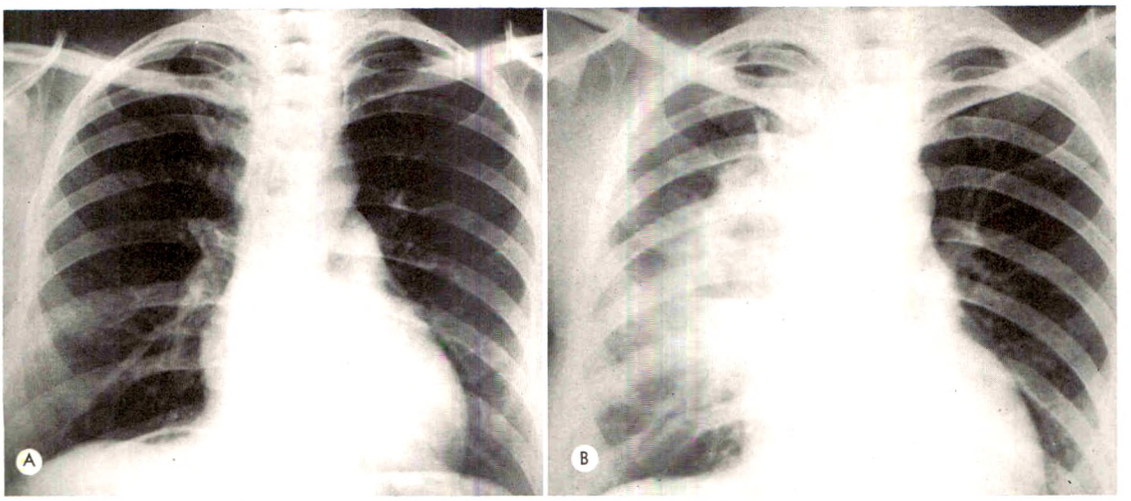


Fig. 1. (*A*) The earliest available chest roentgenogram taken as a routine prenatal examination demonstrated the azygos lobe somewhat denser than normal. (*B*) Four months later the patient developed the pulmonary abscess in the superior segment of the right lower lobe.

chography were performed. Bronchoscopy was unrevealing. Bronchography demonstrated probable areas of bronchiectasis in the apical segment of the right upper lobe. Areas of chronic bronchitic and bronchiectatic changes were also noted in the left lower lobe (Fig. 2). A preliminary barium esophagram demonstrated contrast medium in the azygos lobe (Fig. 3); however, it was not certain that this was not residual from the recent bronchography.

After the lung fields were completely cleared of contrast medium, a repeat barium esophagraphy was performed. The patient was given the medium to swallow in a supine position, and the barium contrast medium was noted to flow into a cystic area of the azygos lobe with the initiation of a coughing spasm (Fig. 4, *A* and *B*). The fistulous tract was better demonstrated in the right posterior oblique position (Fig. 4*C*). Appreciation of the changing caliber of the lumen of the tract was also obtained (Fig. 5, *A*–*D*). Concurrent documentation with cinefluorography demonstrated passage of opaque me-

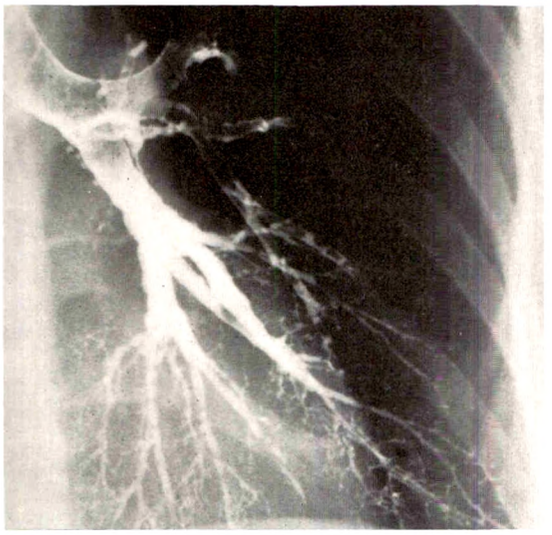


Fig. 2. Bronchiectatic and chronic bronchitic changes in the left lower lobe probably resulted from reaspiration and chronic cough induced from the esophagobronchial fistula to the azygos lobe.

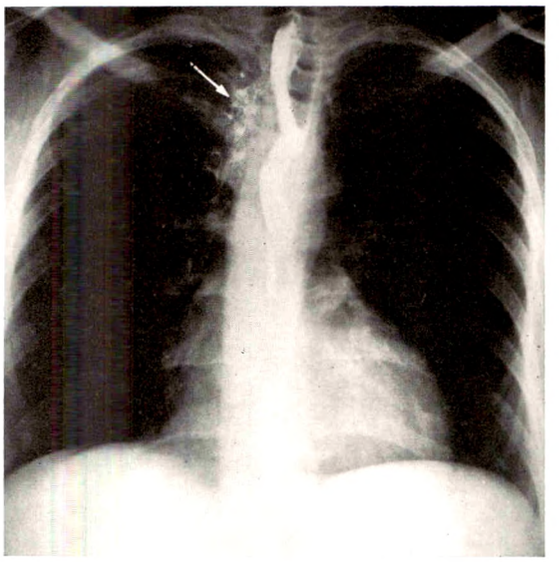


Fig. 3. A preliminary barium esophagram demonstrates contrast medium in the azygos lobe (arrow); however, it was not certain that this was not residual from a recent bronchography.

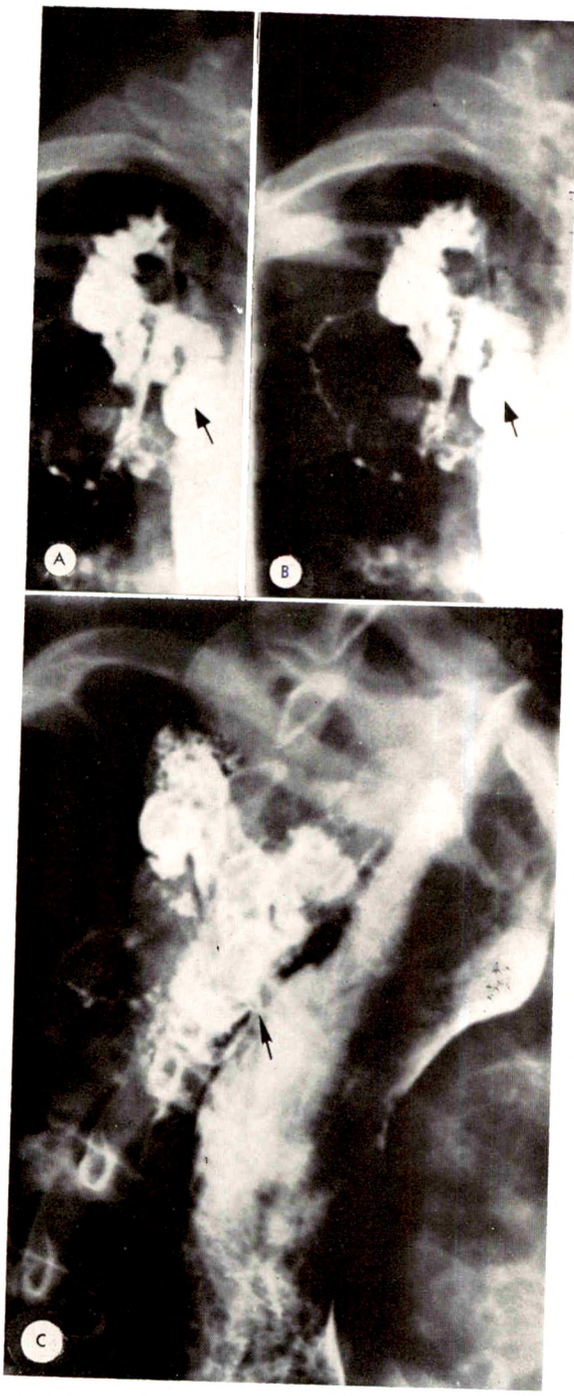


FIG. 4. (*A* and *B*) The patient was given the medium to swallow in the supine position, and the barium contrast medium was noted to flow into a cystic area of the azygos lobe (arrows) with initiation of a coughing spasm. (*C*) The fistulous tract to the azygos lobe was better demonstrated in the right posterior oblique position (arrow).

dium into the fistulous tract and obviated any possibility of aspiration from above the area of fistulization. Esophagoscopy and bronchoscopy were again performed without demonstrating the communication.

A right thoracotomy revealed a fibrous fistulous tract from an esophageal diverticulum to the azygos lobe with extensive surrounding inflammatory adhesions. The azygos lobe and the superior segment of the right lower lobe, which was secondarily involved, were resected. The fistulous tract was approximately 1.5 cm. in diameter and coursed obliquely upwards into the azygos lobe. Within the resected azygos lobe, there were areas of bronchiectasis, atelectasis, abscess formation, and interstitial fibrosis. Microscopically, the tract was lined with squamous epithelium which changed rather abruptly to ciliated respiratory epithelium of a minor bronchus which, in turn, communicated with a cystic cavity similarly lined. The lining epithelium was separated from the adjacent pulmonary parenchyma by a 2–3 mm. wide zone of fibrous tissue which was infiltrated by a moderate number of lymphocytes and a few plasma cells; no smooth muscle cells were present in any portion of the wall of the fistula tract. Culture of the tract and azygos lobe at surgery revealed predominant alpha streptococci, a few non group A beta streptococci colonies, and moderate diphtheroids. No evidence of gummatous or granulomatous tissue was found.

It was felt on the basis of the submucosal fibrotic tissue predominance, evidence of chronic inflammation, and the difficulty of the surgical dissection, that the tract was most likely of acquired inflammatory etiology. However, a congenital origin probably cannot be excluded with absolute certainty as it sometimes is difficult, if not impossible, to separate the original cause.

Following recovery from surgery, the patient has remained well and is asymptomatic.

DISCUSSION

As stated previously, an esophagorespiratory fistula should be considered when the radiologist or clinician is presented with the problem of repeated bouts of respiratory infection or pulmonary symptomatology of obscure etiology.[8,12] This condition can be suspected in any age group.

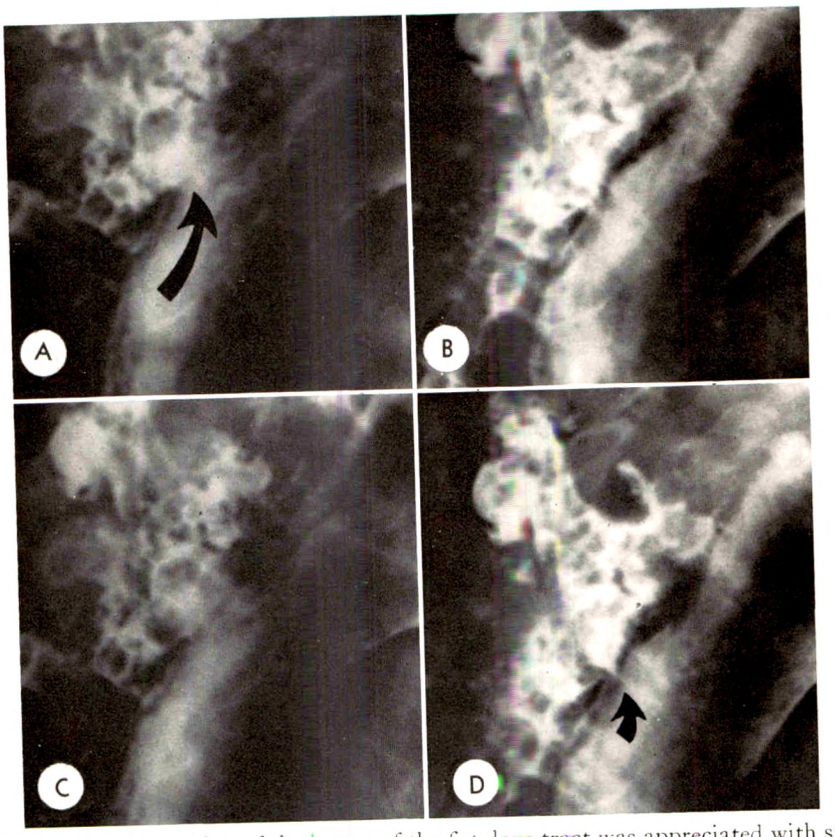


FIG. 5. (*A–D*) The changing caliber of the lumen of the fistulous tract was appreciated with swallowing and breathing. (Small arrow in *D* represents the diminished luminal caliber of the fistulous tract. Large arrow in *A* represents the larger true character of the fistulous tract.)

The patient's history is often revealing with repeated episodes of pneumonitis, cough, and hemoptysis.[8,12] Especially significant is the patient's description of paroxysmal cough being initiated on swallowing liquids or lying in a certain position, placing the tract accessible to oral secretions.[10,11,12] Relief may be obtained by change of position, ingestion of larger particles of food, or taking liquid in a position placing the tract out of access.[10] Indeed, some patients adjust their dietary habits to avoid such aspiration, although the reason is not apparent to them.[10] Particles of food may be raised in the sputum and hemoptysis is a common complaint.[8,12] Whether this is due to the associated tracheobronchitis initiated by aspiration of food and liquid particles into other portions of the bronchial tree, or the secondary occurrence of bronchiectasis, is uncertain (Fig. 2).

Emphasis must be placed on the value of an esophagram in patients with obscure pulmonary disease or suspicious history.[8,10] The diagnosis of either the congenital or acquired esophagobronchial fistula is most often made by the radiologist. Barium swallow study was diagnostic in 65 per cent of the congenital esophagobronchial fistulas.[3] Barium swallow examinations or esophageal ingestion of aqueous contrast agents are more often diagnostic than bronchography, but bronchoscopy will more often permit visualization of the tract than esophagoscopy.[8,10] Methylene blue is helpful in identifying the tract at bronchoscopy after it has been previously instilled into the esophagus and passes by this route into the fistulous connection with the bronchus. The tract may vary in size and patency; repeated examinations with thin barium preparations and in various

positions with contrast medium in the esophagus may be necessary.[6,12] Cinefluoroscopy is particularly valuable to both demonstrate the tract and exclude the possibility of aspiration of medium from other causes such as laryngeal abnormalities.[6] The patient should be placed in the position in which he finds his symptoms most marked, as the tract may otherwise be missed.[14] The 2 categories of bronchoesophageal fistula deserve some elaboration.

ACQUIRED ESOPHAGOBRONCHIAL FISTULA

The acquired esophagobronchial fistula is much more common than the congenital counterpart, and the etiology of acquired esophagobronchial fistula is as below:[1,10]

I. Intrathoracic malignancy—most common cause
II. Infection
  A. Tuberculosis
  B. Fungal
    1. Actinomycosis
    2. Histoplasmosis
  C. Syphilis
  D. Bacterial
III. Trauma
  A. Foreign body ingestion
  B. Instrumentation
  C. Crushing trauma
  D. Operative trauma
  E. Chemical burns

Malignancy in the mediastinum is the most common cause of acquired esophagobronchial fistula.[1,2,10] In one study of 39 cases of esophagorespiratory fistula, 49 per cent were due to malignancy; the rest were due to trauma, tuberculosis, actinomycosis, and esophageal diverticulum (due to peribronchial infections and subsequent fistulous tract formation).[13] Other reviews show an even higher percentage of acquired esophagobronchial fistulas being caused by malignancy.

Hutchin and Lindskog[10] state that the acquired nonmalignant esophagobronchial fistulas are of infectious etiology in two-thirds of cases, and of traumatic etiology in one-third of cases as an approximation. While the cases of fistula due to malignancy are too numerous to warrant tabulation, those of the acquired nonmalignant group number 128 to date, including our own case.[1]

THE CONGENITAL ESOPHAGOBRONCHIAL FISTULA

Braimbridge and Keith[3] reviewed the international literature and found only 23 cases, including 3 of their own, of congenital fistulas between the esophagus and lobar bronchi which were diagnosed in adult life. As stated previously, 65 per cent of these were diagnosed by barium swallow study, and the remaining were discovered at thoracotomy for recurrent pulmonary sepsis. These authors classified the congenital bronchoesophageal fistulas as being of 4 general types:

Type I. Wide-necked congenital diverticulum of the esophagus in which stasis may occur in the dependent tip which becomes inflamed and perforates into the lung. This type, being of partial inflammatory origin, may be difficult to distinguish from the traction diverticulum variety.

Type II. A simple short fistulous tract runs directly from the esophagus to the lobar or segmental bronchus.

Type III. A fistulous tract connecting the esophagus to a cyst in the lobe which, in turn, communicates with the bronchus.

Type IV. The fistula runs into a sequestrated segment of lung which is recognized by the presence of a systemic arterial supply from the aorta. The sequestration connects by one or more tracts with the bronchus.

The embryology of the congenital form of esophagobronchial fistula is in debate.[8] The general theory concerns the embryologic separation of the lung bud at the 5 mm. to 14 mm. embryo stage.[9] It has been suggested that this separation was incomplete, thereby leading to a persistence of a fistulous tract from the esophagus to a pulmonary bronchus. Occasionally, a persistence from a lung bud outgrowth from a lower portion of the foregut, such as a diverticulum or duplication, results in abnormal blood supply and sequestration.[4,8,9]

Other theories regarding congenital enteric respiratory fistula are beyond the scope of this discussion.[8] The theory of these esophagobronchial fistulas developing from persistence of embryologic duplications or diverticulums of the primitive foregut is given some support from cases of congenital duodenobronchial fistulas and biliary bronchial fistulas.[5]

The reasons for the difficulty in demonstrating the fistulous tract and the delayed symptoms to adulthood (ages of the congenital fistulas were from 16 to 55 years) in the congenital variety of esophagobronchial fistula are varied. Briefly, 3 explanations have been offered.[3] One of these subscribes to a membrane which subsequently ruptures, another to a proximal fold of esophageal mucosa initially overlapping the orifice and subsequently becoming less mobile; the third explanation concerns a fistulous tract that runs upwards which may close during swallowing.

SUMMARY

A case of an acquired esophagobronchial fistula to a lesser bronchus of an azygos lobe is presented. The clinical grounds for suspicion of the esophagobronchial fistula in the adult are reviewed, and a summary of the usual varied etiologies of this disorder is presented. Emphasis is placed on the value of the esophagram which is most often the key to this difficult diagnosis. This procedure should be offered to any patient with repeated pulmonary disease or pulmonary symptomatology of obscure origin, as the possibility of cure from distressing symptoms of bronchitis and bronchiectasis may be effected.

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INTRAMURAL ESOPHAGEAL DIVERTICULOSIS*

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A RECENT article by Hodes, Atkins and Hodes[1] prompted this case report. They presented a case of intramural esophageal diverticulosis in a 52 year old male with a 5 year history of dysphagia. It was noted that in 1960 Mendl, McKay and Tanner[2] had reported similar roentgenographic findings in a 56 year old man with dysphagia for 8 months. Mendl *et al.* thought that the esophageal outpouchings were analogous to Rokitansky-Aschoff sinuses in the gallbladder. An addendum to Hodes and co-workers' article stated that in 1954 Dr. Richard Schatzki had reviewed roentgenograms on a case of intramural esophageal diverticulosis. He agreed with Dr. Hodes' group that the findings might represent dilatation of esophageal mucous glands. Either of the above theories would assume a pre-existing process and that these diverticula are acquired.

In March, 1959 we studied the esophagus of a 21 year old male with dysphagia since birth. Esophageal diverticula plus a local stricture was demonstrated. On reading the report of Mendl *et al.*[2] we assumed that the processes were the same. We were able to get the man back in 1961 for a repeat esophagram. He has since been lost to follow-up.

REPORT OF A CASE

B. G. H. unit no. 292407. A 21 year old white male was admitted for esophagoscopy because of dysphagia. This had been evident since infancy. The patient exists on a soft diet and always has.

An esophagram on March 30, 1959 showed a 2 inch area of only moderate stricturing at the sternoclavicular level. Hold-up to fluid barium was minimal. Many intramural diverticula were visualized at the narrowed region. The remainder of the esophagus distal to the stricture showed intramural diverticula in lesser number. These did closely resemble Rokitansky-Aschoff sinuses of the gallbladder (Fig. 1*A*).

Esophagoscopy on March 31, 1959 showed a normal cervical esophagus. A concentric narrowing was noted above the level of the aortic arch. The esophagus could not be visualized distal to the stricture. The mucosa to the area of stricture was normal. The esophagoscopist's impression was that of a congenital stricture of the esophagus. Dilatation to No. 30 French catheter was accomplished without difficulty.

A follow-up esophagram was made on June 27, 1961. The roentgenographic findings were unchanged. The patient's symptoms were the same as before. It is of interest to note that the esophagrams on the case reported by Hodes *et al.* were unchanged over a 3 year period.

DISCUSSION

This case would indicate that if intramural diverticulosis of the esophagus is acquired, it can occur at an early age. Swallowing difficulty was present by history from infancy. The diverticula were at and below the level of narrowing, which would seem to rule out a mechanical pressure factor. There was no evidence of any abnormality of esophageal activity.

Could it be that the diverticula are congenital or developmental and, when complicated by inflammation, dysphagia occurs? In this case there was only one obstructed area. The distal diverticula did not interfere in any way with normal esophageal physiology.

CONCLUSION

1. A fourth case of intramural esophageal diverticulosis is added to the literature.
2. This case also presented with dysphagia.
3. The history and age of the patient

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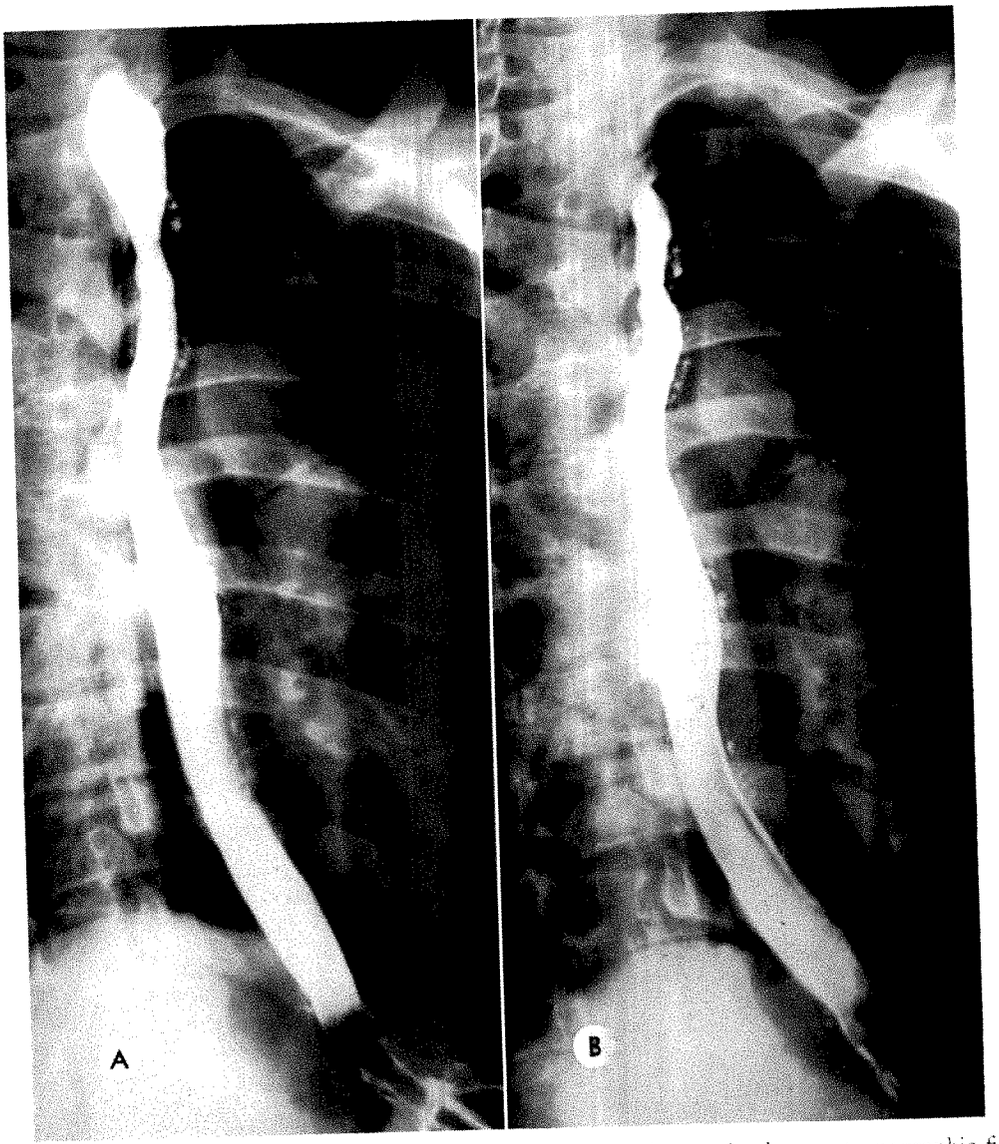


FIG. 1. (*A* and *B*) Esophagrams made 27 months apart show no changes in the roentgenographic findings.

suggest a congenital or developmental origin.

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THE ROENTGENOLOGIC FEATURES OF THE COLUMNAR EPITHELIAL-LINED LOWER ESOPHAGUS*

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THE presence of a columnar-epithelial lining in the lower segment of the esophagus was first described as a distinct pathologic entity by Allison and Johnstone[2] in 1953. Barrett,[3] in 1957, reviewed this subject in detail including etiology, pathologic findings, and therapy. He concluded that the cause of this condition is not known, that the extent of the columnar mucous membrane in the involved esophagus may vary from only a few centimeters above the hiatus to the upper third of the esophagus, and that histologically as well as functionally this columnar epithelium differs from gastric mucosa in that it does not contain parietal or oxyntic cells and secretes little if any acid, pepsin, or secretin.

The lower segment of esophagus lined with columnar epithelium may be seen as an isolated finding in the asymptomatic patient, or it may be found associated with esophageal hiatal hernia.[3]

The diagnosis of columnar-lined lower esophagus depends on the demonstration of columnar epithelium. Roentgenographically, an area of ring-like constriction or stricture marks the squamocolumnar junction, and correlation of cineroentgenographic and endoscopic findings with biopsy above and below the area of constriction will establish the diagnosis.[4,7]

The roentgenographic appearance of the columnar-lined lower esophagus may be confused with benign stricture or short-esophagus hiatal hernia. It is the purpose of the authors to review a series of documented cases of columnar-lined lower esophagus and a large series of cases in which the roentgenologic diagnosis was stricture of the esophagus or short-esophagus hiatal hernia which had roentgenologic features very similar to, and in retrospect may well represent, in some instances, cases of columnar-lined lower esophagus.

MATERIALS AND METHODS

Case material for this study came from 3 categories: (1) those cases in which both the roentgenologic and the endoscopic diagnoses were columnar-lined lower esophagus; (2) cases in which the roentgenologic diagnosis was benign stricture; and (3) cases in which the roentgenologic diagnosis was of short-esophagus hiatal hernia.

There were 9 cases in the first category, 19 cases with roentgenologic diagnosis of benign esophageal stricture, and 127 with roentgenologic diagnosis of short-esophagus hiatal hernia among the case records in the roentgenographic files for the years 1962 and 1963. In 10 of the 19 cases diagnosed as esophageal stricture and in 33 of the 127 cases of short-esophagus hiatal hernia, the roentgenologic features resembled those of columnar-lined lower esophagus on initial inspection, and, therefore, these cases were selected for further study.

OBSERVATIONS IN CASES OF COLUMNAR-LINED LOWER ESOPHAGUS

Cinefluoroscopic Features. Although the diagnosis of columnar-lined lower esophagus was made on the basis of fluoroscopic examination of the esophagus in 9 cases, cinefluoroscopic material was available for study in only 7.

Review of the cinefluoroscopic examinations made in the upright and supine posi-

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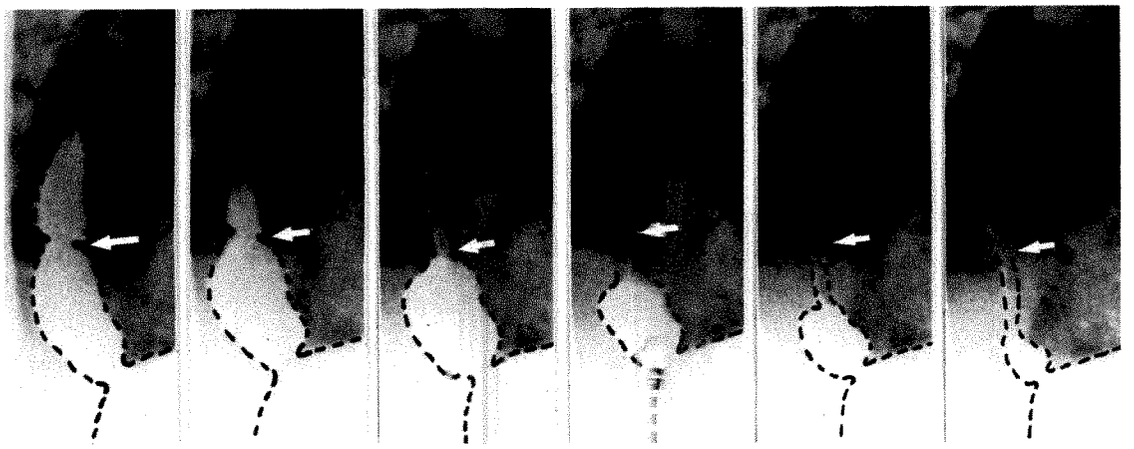


FIG. 1. Cinefluoroscopic demonstration of the peristaltic wave initiated in the upper part of the esophagus passing through the area of constriction (*arrow*) and ending at the muscular esophagogastric junction near the esophageal hiatus.

tions after a swallow of barium revealed that the peristaltic wave initiated in the upper third of the esophagus passed, with only slight hesitation, through an area of stricture or constriction in all cases and continued distally through the esophagus until it reached the muscular esophagogastric junction (Fig. 1). Delay of the peristaltic wave at the site of constriction, as well as transient dilatation of the esophageal segment above the constriction, was a little more pronounced in some cases, and this was seen both in cases of stricture and in cases of constriction. It was clearly evident in all these cases that the segment of digestive tube distal to the area of constriction or stricture was esophageal on the basis of its motor activity as well as its general form and caliber. Motor evidence of hiatal hernia with muscular esophagogastric junction above the hiatus was seen in 4 of the 9 cases.

Roentgenographic Features. Films exposed after fluoroscopic examination in the 9 cases of columnar-lined lower esophagus revealed a ring-like esophageal constriction, 6.5 to 7 cm. from the hiatus in 5 cases (Fig. 2) and a somewhat longer (1 to 2 cm.) stricture, located 4 to 7 cm. from the hiatus in 4 cases (Fig. 3). A small mucosal projection, 2 to 3 mm. in length, was seen in the esophagus on the upper side of the constriction in 2 cases (Fig. 2). This feature was thought to represent ulceration at the time of the initial interpretation, but on endoscopy no ulcer could be seen.

There was no dilatation of the barium-filled esophagus above the constriction or

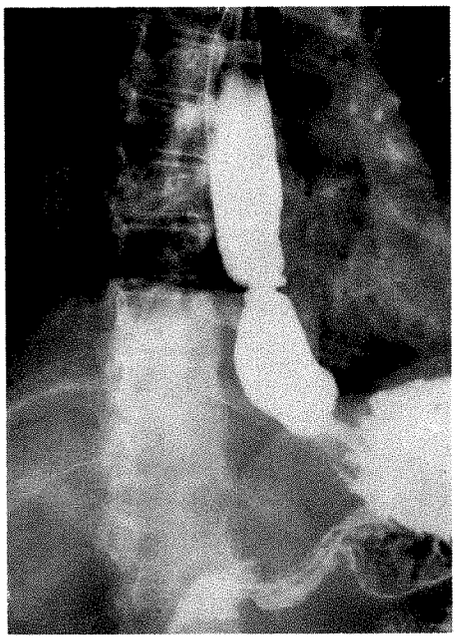


FIG. 2. Same case as in Figure 1. Typical roentgenogram of a columnar-lined lower esophagus demonstrating the mucosal irregularity and the ring-like constriction 7 cm. from the esophageal hiatus. This was previously interpreted as a short-esophagus hiatal hernia with ulceration at the esophagogastric junction. Endoscopy revealed no ulceration at the squamocolumnar junction.

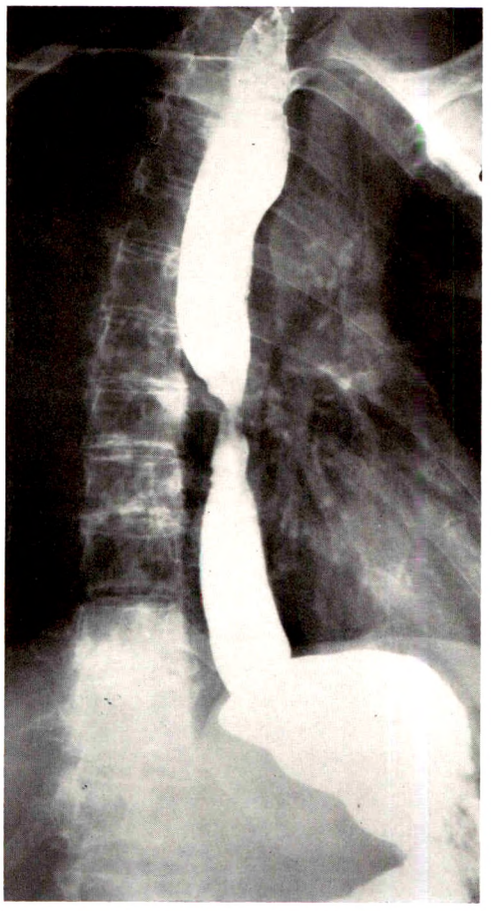


FIG. 3. A strictured segment 2 cm. long, 7 cm. from the esophageal hiatus in a columnar-lined lower esophagus. During fluoroscopy, the peristaltic wave passed through this area with slight hesitation and ended at the muscular esophagogastric junction near the hiatus.

stricture. Esophageal hiatal hernia seen on fluoroscopy in the 4 cases was demonstrated on the roentgenograms.

Endoscopic Findings. Esophagoscopy was performed in 8 cases. In 1 case in which esophagoscopy was not employed, the roentgenologic and fluoroscopic features were those of the columnar-lined lower esophagus, and this observation was further substantiated by motility studies. The area of ring-like constriction or somewhat longer stricture was visualized in all cases. Biopsy of a specimen from just below the stricture in 4 cases and just below the ring-like constriction in 3 cases showed columnar epithelium. Review of the biopsy specimens revealed the presence of parietal cells in 3 instances and inflammatory gastric mucosa without parietal cells in the others. The ring-like constriction seen roentgenologically was thought on endoscopic examination to represent the squamocolumnar mucosal junction because of the transition of the mucous membrane from flat, squamous type to that of velvety, more pinkish columnar type at a distance from the incisor teeth corresponding to the location of the ring. This was confirmed by biopsy in 3 of the 5 cases with the relatively localized constriction.

Clinical Features. Four patients had dysphagia of 2 to 5 years' duration, and all 4 had strictures which were somewhat longer and narrower than the ring-like constriction described above. In 1 patient the stricture was associated with a large hiatal hernia with the stomach beginning 4 cm. distal to the stricture. None of the 5 patients who had ring-like constrictions had dysphagia.

RETROSPECTIVE STUDY OF STRICTURES

Roentgenographic Features. In 4 of the 10 cases of benign stricture of the esophagus with roentgenographic features similar to those of the columnar-lined lower esophagus, the initial roentgenologic diagnosis was benign stricture, and in 6 it was stricture with short-esophagus hiatal hernia. In retrospect, however, the part of the alimentary tract distal to the stricture in these 6 patients had the form and caliber of the esophagus rather than those of the stomach.

In 3 of the 10 cases, the strictures were located in the upper third of the esophagus, in 3 in the middle, and in 4 in the lower third. The length of the strictures ranged from 0.5 to 4 cm. and averaged 2.5 cm., with tapering of both the proximal and the distal portions of the esophagus near the stricture. There was no esophageal dilatation proximal to the strictured segment. Associated obvious hiatal hernia was present in 2 cases, and in both cases the strictures were located in the upper part of the esophagus, well above the muscular esophagogastric junction.

Endoscopic Findings. Esophagoscopy

was performed in all 10 cases, with biopsy in 7. In the majority of cases, passage of the esophagoscope through the strictured segment presented some difficulty. Histologic examination of a specimen removed just below this level revealed inflammatory columnar mucosa in 5 cases and inflammatory tissue only in 2.

Clinical Features. There were 6 females and 4 males in this group, ranging in age from 27 to 71 years with an average age of 53 years. All had dysphagia of moderate to marked severity, usually of long duration. Two patients gave a history of dysphagia since early childhood.

RETROSPECTIVE STUDY OF SHORT-ESOPHAGUS HIATAL HERNIA

Roentgenographic Features. In 33 of 127 cases in which the roentgenologic diagnosis of short-esophagus hiatal hernia had been made previously, the roentgenographic appearance was suggestive of columnar-lined lower esophagus. At least 3 roentgenograms made for the demonstration of the distal three-fourths of the esophagus, as well as the esophagogastric junction, were available in all cases, but no cinefluoroscopic sequence was available for review.

A ring-like constriction was present in the distal segment of the esophagus in all 33 cases. This constriction was not completely symmetric, and its shape varied somewhat, depending on the projection and amount of barium in the esophagus at the time the roentgenogram was made.

In all cases the distance between the constriction and the esophageal hiatus was 4 to 8 cm. Small mucosal projections as previously described were seen in 10 cases. In an additional 2 cases, the roentgenographic features were those of scleroderma involving the esophagus; this diagnosis was confirmed later by motility studies in 1 case. In 5 cases the muscular esophagogastric junction, as judged roentgenographically, was located above the hiatus, and the stomach obviously began 4 to 5 cm. distal to the ring-like constriction.

Endoscopic Findings. Esophagoscopy was performed in 13 cases, with biopsy in 9. In those in which measurements were recorded, the mucosal esophagogastric junction was thought to be 33 to 35 cm. (13 to 14 inches) from the upper incisor teeth, on the basis of mucosal transition from squamous to columnar epithelium. In 7 cases, biopsy of tissue removed from below the constriction revealed columnar mucosa and, in 2, inflammatory tissue.

Clinical Features. The 19 males and 14 females in this category varied in age from 33 to 72 years and averaged 59 years of age.

A majority of the patients were asymptomatic, and in only 13 cases was a history of dysphagia noted. Dysphagia, when present, was of a mild nature and did not constitute the patient's primary complaint.

DISCUSSION

Columnar-lined lower esophagus (Barrett esophagus) is probably more prevalent than it was previously thought to be. The number of reported cases, however, is small, and well-documented clinical courses as well as pathologic studies are lacking. The cause of this condition is not definitely known, both congenital and acquired theories have been proposed.[1,3]

The diagnosis of columnar-lined lower esophagus depends on the correlation of fluoroscopic or cinefluoroscopic examination of the esophagus, with endoscopic examination and biopsy of the mucosa above and below the constriction or stricture.

On roentgenologic examination of the esophagus, it is essential that one observe the motor activity of the esophagus with the barium swallow and follow the primary peristaltic wave which is initiated in the upper third of the esophagus and which terminates at the muscular esophagogastric junction. In cases of columnar-lined lower esophagus with ring-like constriction or stricture at the mucosal squamocolumnar junction, the peristaltic wave will pass through this area, with slight hesitation, as well as through the segment of gut distal to this point, and terminate at the muscular esophagogastric junction, which may be at the level of the hiatus or above the hiatus, depending on the presence or ab-

sence of an esophageal hiatal hernia. On the roentgenogram there is an area of constriction well above the esophageal hiatus or, in cases associated with hiatal hernia, above the muscular esophagogastric junction. This feature is best demonstrated with the patient in the supine position when the esophagus is well distended with contrast material. In about a third of the cases, a small mucosal projection may be seen just above the area of constriction and should not be considered ulceration. Mucosal projections were not seen in cases of stricture. The roentgenologic appearance of the segment of the digestive tube below the constricted area is that of the esophagus, as judged by motor activity, shape, and caliber.

Thus, columnar-lined lower esophagus may be seen in two forms. In the first form, the squamocolumnar junction is marked by a ring-like constriction some distance away from the muscular esophagogastric junction, and in the second form, the squamocolumnar junction is represented by a somewhat longer (1 to 2 cm.) stricture. Of our total group of 52 patients studied, 14 had strictures and 38 a ring-like constriction at the squamocolumnar junction.

Pierce and Creamer[7] reported on 6 cases of columnar-lined lower esophagus. Hiatal hernia and esophagitis were present in all of their cases. In our series, definite hiatal hernia was seen only in 4 of the 9 documented cases of columnar-lined lower esophagus and in 5 of the 33 cases of "short-esophagus hiatal hernia" reviewed in which roentgenographic features were very suggestive of columnar-lined lower esophagus.

Some authors have stated that columnar-lined lower esophagus is not recognizable by roentgenologic methods in the absence of inflammatory complications and also may be overlooked on esophagoscopy.[8] The majority of our patients with well-documented columnar-lined lower esophagus and those given an initial roentgen diagnosis of short-esophagus hiatal hernia were relatively asymptomatic at the time of the roentgenologic examination. The patients with the somewhat longer stricture were the exceptions to this.

Although Barrett[3] stated that the columnar mucosa near the junction did not contain parietal cells, biopsy specimens from 3 of our 7 patients with the characteristic fluoroscopic and endoscopic appearances of a columnar-lined lower esophagus did reveal the presence of these cells. A critical evaluation of this feature, however, would probably require the availability of specimens from extensive resection or autopsy, and such specimens were not available in these cases. Our findings would be in keeping with Jones and Gummer's[6] statement that the mucous membrane lining such an esophagus produces both acid and pepsin and may develop a typical gastric ulcer as well as adenocarcinoma. Hershfield and associates[5] recently reported on an interesting patient with a columnar epithelium-lined lower esophagus in whom they demonstrated the secretion of hydrochloric acid from this esophageal segment. The patient died of adenocarcinoma arising near the squamocolumnar junction in the midesophagus, and autopsy revealed that the columnar epithelium in the lower part of the esophagus contained both parietal and pepsinogen granule cells.

Motility studies of the esophagus also will confirm the motor activity of the lower segment as esophageal and not gastric in type. Cohen and associates[4] reported no discontinuity of esophageal motor function when measurements were made through the squamocolumnar junction in a case of columnar-lined lower esophagus. Esophageal motility was studied in 2 cases with columnar-lined lower esophagus in our total series, and the motor function of the segment below the constriction was esophageal.

Columnar-lined lower esophagus can be confused with benign stricture or short-esophagus hiatal hernia with the area of the constriction thought to be the muscular esophagogastric junction. In case of stricture, differentiation depends entirely on esophagoscopy and biopsy, as both inflam-

matory stricture and columnar-lined lower esophagus with stricture may look alike cinefluoroscopically. Differentiation of columnar-lined lower esophagus from short-esophagus hiatal hernia should not be difficult (Fig. 4). The fluoroscopic observation of the peristaltic wave passing through the area of constriction should indicate that the segment below this area is esophagus and not stomach. The association of columnar-lined lower esophagus and hiatal hernia is not uncommon and when present can best be demonstrated by cinefluoroscopy.

Clinically, patients with columnar-lined lower esophagus with stricture at the squamocolumnar junction will have symptoms of dysphagia. Patients with an area of ring-like constriction only, however, may be entirely asymptomatic. As a result, this condition may be an incidental finding on routine roentgenologic examination of the upper part of the gastrointestinal tract.

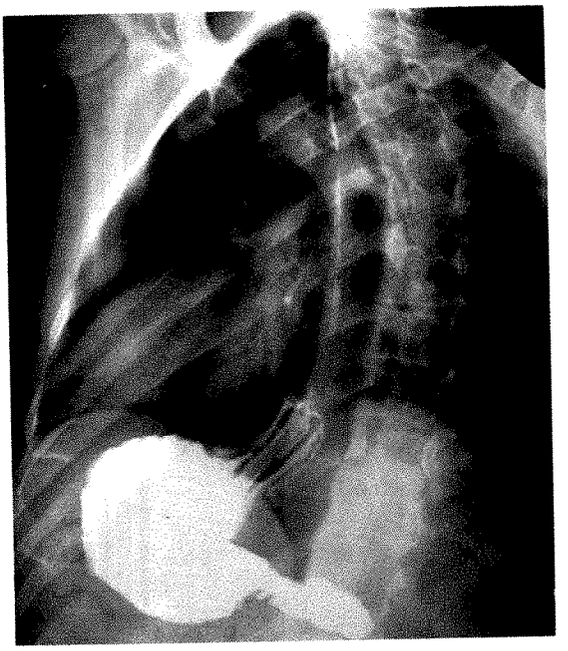


FIG. 4. Typical roentgenographic appearance of short-esophagus hiatal hernia. The peristaltic wave in this case stopped 5 cm. above the esophageal hiatus marking the muscular esophagogastric junction.

SUMMARY

Diagnosis of columnar-lined lower esophagus depends on correlation of fluoroscopic or cinefluoroscopic examination of the esophagus with endoscopic study and biopsy. Columnar-lined lower esophagus may be seen in two forms. The squamocolumnar junction may be a tapered, strictured segment or a ring-like constriction some distance away from the muscular esophagogastric junction. Fluoroscopic and cinefluoroscopic study of the motor function of the esophagus in cases of strictures or ringlike constrictions will yield the evidence for differentiating this condition from short-esophagus hiatal hernia.

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THE ROENTGEN DIAGNOSIS OF DIFFUSE ESOPHAGEAL SPASM*

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ROENTGENOLOGIC abnormalities which suggest motor disturbances of the esophagus are encountered in both symptomatic and asymptomatic subjects. The interpretation and evaluation of these roentgen changes in terms of their clinical significance often present a difficult problem to the clinician and the roentgenologist. A source of additional difficulty stems from the variety of terms by which the abnormal roentgen images have been designated. These terms include "tertiary contractions," "curling," "tiered spasms," "elevator esophagus," "rosary bead esophagus," "presbyesophagus," "corkscrew esophagus" and "diffuse esophageal spasm" among others. Each designation carries its own vague and often ambiguous implication of a normal finding, of a normal variant or of disordered function and disease. Recent studies of esophageal physiology employing both roentgen and intraluminal pressure techniques have helped to clarify some of the problems. In this discussion, concepts established with the aid of intraluminal manometry will be correlated with roentgen changes. It is felt that fluoroscopic observation of the movements of the esophagus, based upon a knowledge of the normal, will suffice for an accurate diagnosis of a motor abnormality of the esophagus. Complicated manometric studies requiring expensive equipment are considered unnecessary.

NORMAL ESOPHAGEAL FUNCTION

PRIMARY PERISTALSIS

As a bolus is ejected from the buccal cavity into the hypopharynx, a chain of events known as primary peristalsis is initiated. As the bolus enters the hypopharynx the esophagus is prepared to receive it by relaxation of both the upper and lower esophageal sphincters.[3,4] The bolus is then propelled distally into the esophagus by the contraction of the hypopharyngeal musculature. Once the bolus has entered the esophagus, it is moved along by a *peristaltic wave* beginning at the upper esophageal sphincter and traveling toward the stomach at a rate of 2 to 4 cm. per second.[2] This propulsive wave carries the bolus through the lower esophageal sphincter into the stomach. If pressure recording catheters are placed in the esophagus and the esophageal activity is recorded, the following pattern is obtained: In the resting state, the intraluminal pressure in the body of the esophagus varies between 0 and −4 mm. of mercury, depending on the phase of respiration. At each end, the lumen of the esophagus is closed off by the tonic contraction of a short segment. These segments constitute the upper and lower esophageal sphincters. Within 0.2 to 0.6 seconds following the initiation of a swallow, the upper sphincter relaxes, while the lower sphincter relaxes within 1.5 to 2.5 seconds of deglutition. Simultaneously with the relaxation of the sphincters, the peristaltic wave which follows is recorded manometrically as a "spike-like" increase in intraluminal pressure of 40 to 80 mm. of mercury[1] extending over a 4 to 8 cm. segment of the esophagus and traveling distally at a rate of 2 to 4 cm. per second, depending on the consistency of the bolus. When the peristaltic wave has passed through the lower end of the esophagus, the lower esophageal sphincter resumes its closed position.

SECONDARY PERISTALSIS

If some material should remain in the esophagus following the passage of the pri-

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mary peristaltic wave or if material is regurgitated from the stomach into the esophagus, a lumen-obliterating wave of peristalsis is seen to begin in the area of the upper sphincter, pass down the esophagus and sweep the contents into the stomach. Intraluminal pressure measurements of this wave, known as secondary peristalsis, reveal a pattern which is identical with primary peristalsis. Thus, primary and secondary peristalsis are identical roentgenologically and manometrically, but differ in that the primary type is initiated by swallowing while the secondary type is initiated by stimuli acting locally on the esophageal wall.

FLUOROSCOPIC APPEARANCE OF PRIMARY PERISTALSIS

When a single mouthful of liquid barium is swallowed, the bolus fills almost the entire length of the esophagus in a continuous column extending from the hypopharynx to the lower esophagus. After a momentary delay, the barium begins to enter the stomach. As the act of swallowing is completed a lumen-obliterating wave of peristaltic contraction moves down the esophagus from the upper to the lower sphincter at a speed of 2 to 4 cm. per second. Thus, the normally functioning esophagus exhibits (1) relaxation of both sphincters followed by (2) primary peristalsis which sweeps down the esophagus and carries the esophageal contents into the stomach. These two components of normal swallowing may be readily observed by fluoroscopic examination (Fig. 1).



Fig. 1. *Normal esophagus:* A primary peristaltic wave (arrows) is observed as a component of each complete act of swallowing in the normal subject.

ABNORMAL ESOPHAGEAL FUNCTION

CURLING OF THE ESOPHAGUS

The descriptive term "curling" for spontaneous contractions (as opposed to peristalsis) which are induced or stimulated by a bolus of sufficient bulk to distend the esophagus maximally was introduced by Schatzki[7] who likened the roentgen appearance of the esophagus to curling of hair. These contractions are seen particularly in the older age group and manifest themselves as a series of ring-like contractions of the distal esophagus. In its mild form, curling of the esophagus produces no symptoms, but in its more severe form it is usually associated with the clinical syndrome of diffuse esophageal spasm.[6] The "curling" phenomenon is often referred to in the literature as "tertiary contractions" even when diffuse spasm is being discussed.[8] In asymptomatic individuals exhibiting the curling phenomenon, primary peristalsis, is usually present, whereas it is absent in subjects with symptoms (Fig. 2). In the latter, normal primary peristalsis is replaced by multiple, simultaneous, nonpropulsive contractions.[6]

DIFFUSE ESOPHAGEAL SPASM

Diffuse spasm of the esophagus is a clinico-roentgenologic syndrome comprised of intermittent dysphagia, retrosternal pain and abnormal esophageal contractions. In this disorder, both sphincters open in response to swallowing and barium is distributed throughout the entire length of the esophagus as in the normal individual. However, the primary peristaltic wave moves down the esophagus only to the

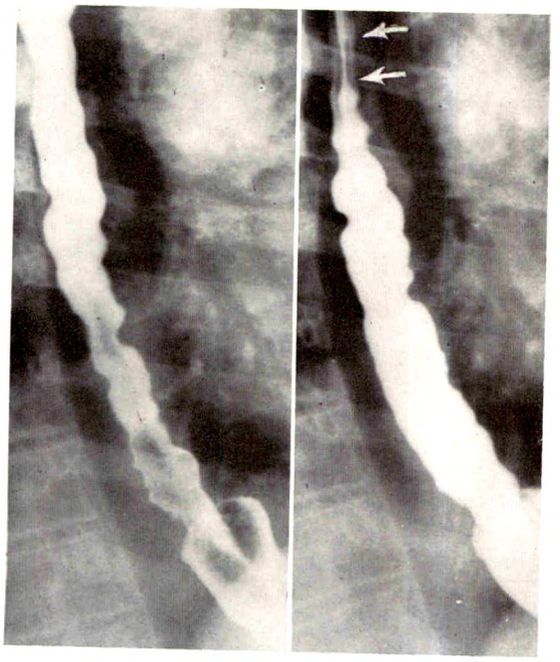


FIG. 2. *"Tertiary" contractions:* Roentgenograms made during fluoroscopic study of an elderly female with vague symptoms of chest pain on exertion. A wave of primary peristalsis has begun to traverse the esophagus (arrows). This type of peristalsis is not observed in patients with diffuse spasm but will be seen with tertiary contractions.

level of the aortic arch, where it falters and its forward progession is halted. Thus, barium remains in the lower esophagus, unable to move into the stomach. However, as the lumen of the lower two-thirds of the esophagus becomes distended by the passive accumulation of barium reaching it from above, a critical point of distention is reached at which the lower esophagus *contracts* diffusely over its entire length. (It should be emphasized that this is *contraction* [a local phenomenon] as contrasted with *peristalsis* [a coordinated wave of contraction].) The roentgenologic changes which are seen in diffuse esophageal spasm are areas of contraction (narrowed areas) alternating with areas of dilatation (ballooned-out areas). It is this roentgenologic appearance which has been termed the "rosary bead" esophagus, "tiered spasms" and "pseudodiverticulosis" and is also known by other names. As the lower two-thirds of the esophagus contracts, barium is regurgitated into the proximal portion of the esophagus above the level of the aortic arch, whereupon a second wave of peristalsis (secondary peristalsis) sweeps the barium downward out of the upper one-third. However, the second wave also falters at the level of the aortic arch. Thus, the cycle is repeated over and over again. Pressure recordings in diffuse esophageal spasm confirm this cycle of events, revealing that in response to a swallow both esophageal sphincters relax and that peri-

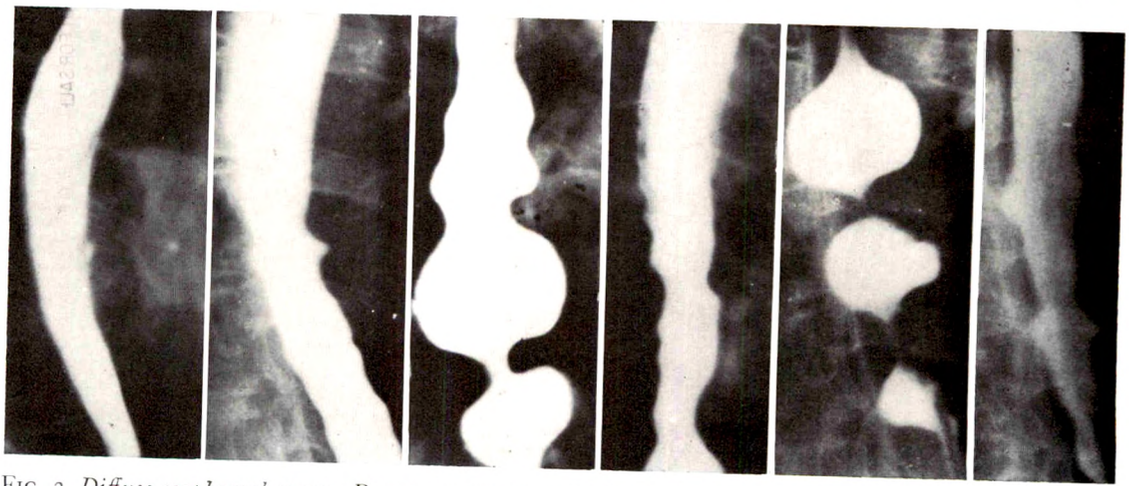


FIG. 3. *Diffuse esophageal spasm:* Roentgenograms made during fluoroscopic study of a 58 year old female who complained of severe substernal chest pain associated with swallowing. Note the variability in the appearance of the abnormal contractions. Primary peristalsis was not observed although many examinations over several months were performed.

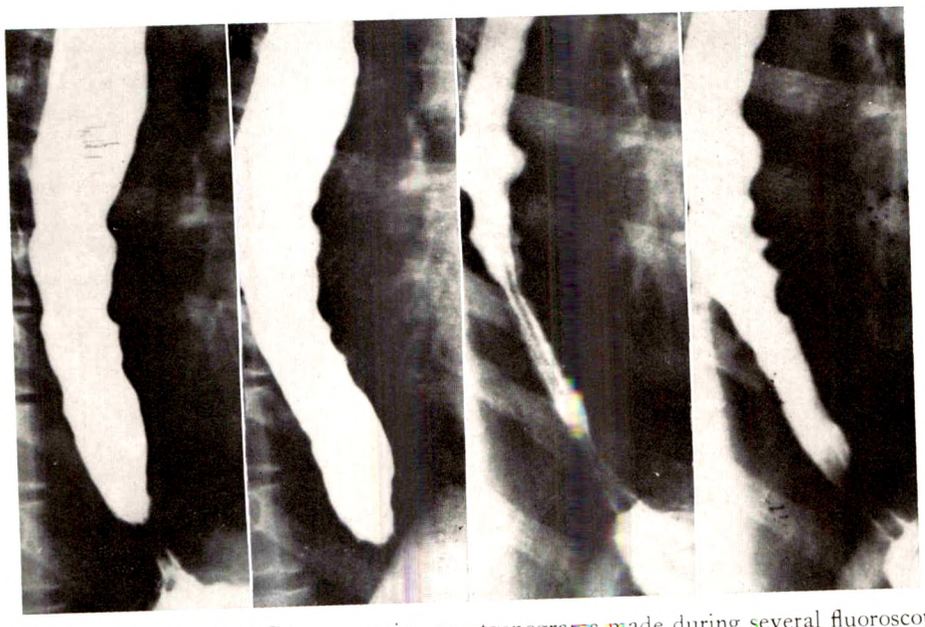


Fig. 4. *Diffuse esophageal spasm:* Representative roentgenograms made during several fluoroscopic studies of a 52 year old woman who complained of severe dysphagia associated with substernal pain. Primary peristalsis was not observed during any of the examinations.

stalsis begins at the upper sphincter and sweeps down the esophagus at a normal rate of speed. As the peristaltic wave reaches the arch of the aorta, this primary wave of peristalsis is replaced by simultaneous, repetitive contractions occurring ("diffusely") over the entire lower portion of the esophagus (Fig. 3 and 4).

Considerable confusion has resulted from statements appearing in the literature to the effect that patients suffering from diffuse spasm will occasionally exhibit a normal esophagus on roentgen examination. It has been our experience that once diffuse spasm is observed, it can always be demonstrated thereafter. If the esophagus is not examined carefully and the peristaltic movement followed over the entire length of the esophagus, the failure of progression of the primary peristaltic wave will be missed. The characteristic areas of contraction alternating with dilatation may not appear if care is not taken to give barium in sufficient bulk to distend the lumen of the esophagus below the aortic arch to the critical level so that a sufficiently strong stimulus to the contractions is produced.

Recent reports maintain that the use of both roentgen study and intraluminal pressure measurements is essential for the diagnosis of diffuse spasm. However, the recording of motility by this means requires the use of complicated and expensive equipment. It is our opinion that manometry is unnecessary and that the diagnosis can be made solely by roentgen methods, especially careful fluoroscopy, provided the examination is based upon a knowledge of normal esophageal function.

Roentgen Technique for Demonstration of Diffuse Esophageal Spasm

The following procedure is recommended for the demonstration of diffuse esophageal spasm:

Patients are examined in the standing position and are given a large bolus of liquid barium. The ease with which the barium mixture flows through the esophagus is observed. At the end of a swallow, the upper esophagus is observed for peristalsis. If none is elicited, the patient is given a larger bolus of barium. Again, if peristalsis is absent, the patient is placed in the supine position and fed a thick barium

paste. As this mixture enters the esophagus, it can only be propelled distally by peristalsis as the factor of gravity has been removed. In diffuse spasm, peristalsis will move the bolus of barium only to the level of the aortic arch below which the bolus will then accumulate and gradually distend the lumen. As the critical point of distention is reached, the esophagus will suddenly go into spasm and reveal the characteristic appearance of areas of contraction alternating with areas of dilatation. The barium is thus regurgitated into the upper esophagus. Secondary peristalsis carries the material out of the upper third into the lower esophagus and the cycle repeats itself.

SUMMARY

1. The roentgenographic and physiologic features of the normal swallowing complex have been reviewed and are related to roentgen manifestations of motor dysfunction, notably diffuse esophageal spasm.

2. A roentgen technique for demonstrating diffuse esophageal spasm is described.

   a. The important point in this technique is that sufficient barium must be given to ensure maximal esophageal distention, which is a requisite for the stimulation of the abnormal contractions.

   b. The cardinal observation to be made fluoroscopically is the absence of peristalsis in these patients.

3. The view has been expressed that diffuse spasm should be diagnosed by proper roentgen techniques alone. Complicated motility measurements are considered unnecessary.

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Vol. 99, No. 1

THE "CAPTIVE BOLUS" TEST AND THE PINCHCOCK AT THE DIAPHRAGM*

AN ESOPHAGEAL PUMP AND SOME NON-DISEASES OF THE ESOPHAGUS

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IT SHOULD be stated at the outset that the "captive bolus" test is not primarily a test *for* any particular entity—rather it is a test *of*. The *of* applies to a variety of proposed mechanisms, theories and observations involving certain phenomena which are encountered in and about the distal esophagus. Moreover, the test is not really new in that the familiar Valsalva maneuver is used to elicit the phenomena to be mentioned and even these have been, in part, described by Templeton,[20] Vandervelde and Carlson[21] and others.

I am hopeful, however, that a fresh way of looking at some of the interesting configurations observed in this region may aid a better understanding of the mechanisms which apply to it.

METHOD

In the prone (right anterior oblique) position the patient takes one swallow of barium and immediately after swallowing takes a deep breath, holds it, and makes a maximum *sustained* straining effort. The test may also be performed in the upright position.

In the normal patient there is either a slight tenting of the fundus into the hiatus or no particular change in morphology occurs and the esophagus empties completely or nearly so with the first peristaltic wave.

In a patient with a positive test, the barium column is pinched off at and for a variable distance above the diaphragm. This constriction, of course, is the so-called diaphragmatic pinchcock. A peristaltic wave then forms in the esophagus and advances at a uniform rate of about 4 cm. per second forcing barium ahead of it until it reaches the physiologic sphincter, continues to the lower margin of the sphincter and stops. The sphincter remains in tonic contraction for a variable length of time. Trapped between the sphincter and the diaphragmatic pinchcock is a bolus of barium which varies in size according to the height of the cone of the phrenoesophageal ligament. This is the "captive bolus."

The pressure produced by the advancing peristaltic wave may force the diaphragmatic pinchcock as long as the wave is being promulgated, but as the wave cannot advance beyond the sphincter itself, the barium present when the wave reaches its endpoint cannot be evacuated as there is no peristalsis in the "herniated" fundus of the stomach or in a 1–3 cm. segment of the esophagus distal to the sphincter.

At this point, the situation is unstable and something has to give. Either the patient can no longer sustain the Valsalva test or the physiologic sphincter cannot maintain its contraction. Should the latter occur, a powerful jet is released the instant the sphincter tone is overcome, resulting in a spurt of barium to the level of the aortic arch or above in as little as 1 or 2 sevenths of a second. At first, the jet has a caliber of only 3–4 mm. but it broadens rapidly as the captive bolus is released and ejected into the proximal esophagus. Within 1.5 seconds, the esophagus is refilled from below. If the observer's attention is directed to the portion of the esophagus above the captive bolus he will have the impression of reverse peristalsis; however, this is not at all the

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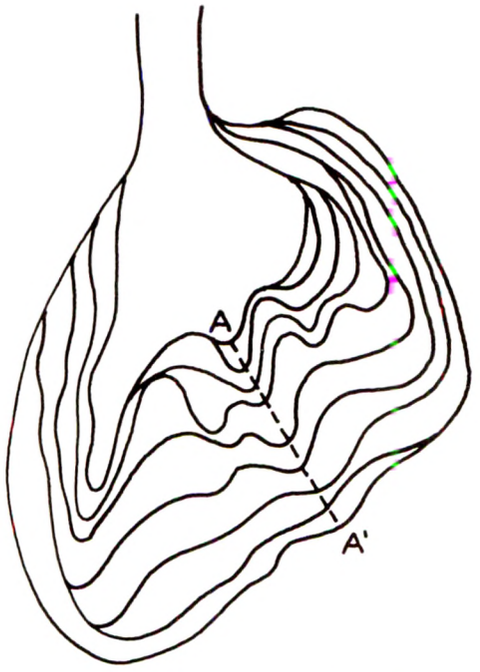


FIG. 1. Serial tracings of a cine-strip of the collapse of the "captive bolus," 7.5 frames/sec. As the barium is ejected proximally into the esophagus, the pinchcock zone increases in length, the pouch becomes deeply concave with its lower margin moving upward with greater rapidity and greater amplitude than the motion of the side walls. The lengths of the outer and inner tracings are nearly equal if the line A-A′ is traced and re-traced. This appearance indicates that a mass is sliding through the hiatus, pushing the barium contained in the herniated stomach ahead of it with considerable force.

case. Cine-films of this phenomenon centered on the pouch containing the bolus show that it collapses in its axial direction before its transverse diameter becomes appreciably diminished—as though a piston were moving up from below, ejecting barium ahead of it.

If the patient is able to sustain the Valsalva effort, a new peristaltic wave will form and once again force the regurgitated barium into the compartment between the sphincter and the pinchcock. Repeated cycles of this nature may be followed without so much as a drop of barium being forced through the pinchcock.

With certain exceptions to be noted later, this test is in some form "positive" in all patients with sliding hiatus hernia when this diagnosis can be made by any of the now numerous signs. It is also clearly positive in many patients showing equivocal signs and in a number of patients who do not display any of the commonly accepted morphologic criteria of hiatus hernia.

THE PINCHCOCK AND THE PUMP

Before describing the atypical modifications of the test, it seems appropriate to consider some of the questions raised by the phenomena it elicits. Of course, the most interesting of these questions is the nature of the "pump." Serial tracings of cine-frames when superimposed (Fig. 1) show much the appearance of successive phases in the action of a bulb syringe as the lower outline of the captive bolus becomes progressively more proximally situated and progressively more concave as it empties. In keeping with this type of action is the observation that if the lengths of the outermost and innermost tracings are measured they are equal within about 10 per cent if the length of line A–A′ in Figure 1 is included. However, the inner outline is much smaller than the outer if one does not include this line. It is also apparent that a considerable pressure is developed in the captive bolus to cause such a rapid ejection of barium the instant the physiologic sphincter releases.

To understand the nature of this "pump," it is necessary to reconsider the pinchcock action at the diaphragm (Fig. 2, *A–D*). For many years the views summarized by Collis *et al.*[5] have been widely accepted. It is held that reflux is prevented by: (1) the obliquity of insertion of the esophagus into the stomach; (2) the sling fibers of the stomach; (3) the muscle of the right crus; and (4) the supposedly "weak" sphincter at the lower end of the esophagus. In some way never clearly specified, the summation of these effects has been considered to form a pinchcock action. This action, although a somewhat controversial effect among radiologists, to most surgeons is the theoretic underpinning for much of the reparative work done about the hiatus. However, Dornhurst, Harrison and Pierce[7]

are so convinced, rightly I believe, that the diaphragm cannot exert a pinchcock action that they have gone so far as to deny the existence of a pinchcock. Johnstone,[13] while conceding the weakness of the conventional arguments concluded, "Surely there is no other explanation for the constriction of the stomach in the hiatal canal which occurs with inspiration." Clearly, what is needed is a theory more in accord with observation.

To begin with, the pinchcock is an undeniable phenomenon even though it cannot be seen in every case. In searching for examples (and the captive bolus test is ideal for the purpose), it soon appears that the pinchcock can be demonstrated only *in patients who have sliding hiatus hernias*. Moreover, such patients when re-examined after a successful hiatus hernia repair no longer have a diaphragmatic pinchcock. It is a curious paradox that the surgeon who sets out to "restore the diaphragmatic pinchcock" destroys what he intended to restore and yet succeeds in spite of himself.

A second observation bearing on the problem is the circumstance that the gastric tube is compressed *above* the hiatus. Moreover, the thickness of the diaphragm is of the order of millimeters, whereas the length of the constriction is of the order of centimeters—a finding clearly inconsistent with the thesis that the crura play an effective role.

Together, these observations establish that there must be a stretched, elongated phrenoesophageal ligament before a pinchcock mechanism can be set up. The tension produced by the tone of the longitudinal muscle of the esophagus causes the ligament to take the shape of a conical "tent." The studies of Zaino, Poppel, Jacobson, Lepow and Osturk[23] have confirmed that the phrenoesophageal ligament inserts at the cardioesophageal junction, bifurcating to send fibers above and below it. This mucosal junction then must occur at or very close to the vertex of the cone. Passing through the conical tent in the position of the "tent pole" is the retracted cardiac end of the stomach. Simple hydro-mechanical principles now predict exactly what will occur when the increased intra-abdominal pressure produced by straining forces abdominal contents* into the base of this cone. The walls of the cone will bulge in a more or less hemispherical fashion and the walls of the gastric tube passing through the cone will bulge inward and pinch off the lumen. The explanation for the pump action now becomes clear: Protrusion of abdominal contents into the base of the "tent" provides the driving action of the pump as these tissues elongate the pinchcock. The action is analogous to a mechanism used in mechanical cardiac pumps which develop a pressure by having a roller or a pair of rollers milk a rubber tube by rolling along it, except that a toroidal roller action is postulated here (Fig. 3).

Because of the close analogy to an artificial cardiac pump and because of its location at the cardiac end of the stomach, it would seem appropriate to name this pumping mechanism the "cardiac pump." Unfortunately, the name has been preempted by a nearby and better known propulsive organ.

PINCHCOCK MECHANICS

The efficacy of the pinchcock depends on:

1. The patient's ability to sustain an expiratory effort. Thus the aged or the mentally impaired are not good subjects for eliciting these phenomena.
2. The length of the phrenoesophageal ligament. There is a critical minimum of relaxation or stretching required before an effective mechanism can be set up.
3. Esophageal shortening. If the cone is inverted (apex down) or cannot form, there is no pinchcock action.

No matter how stretched the phrenoesophageal ligament may be, the pinchcock mechanism, captive bolus and hydraulic pump mechanism cannot exist if the longi-

* Sandmark[18] clearly envisioned the possibility that abdominal contents could be forced through the hiatus and constrict the herniated stomach. His preoccupation with pressure and density relationships and neglect of the phrenoesophageal ligament prevented him from drawing many verifiable inferences from this insight. It is most instructive to repeat his mechanical experiments either as "thought experiments" or in actuality after making the necessary modifications in his apparatus.

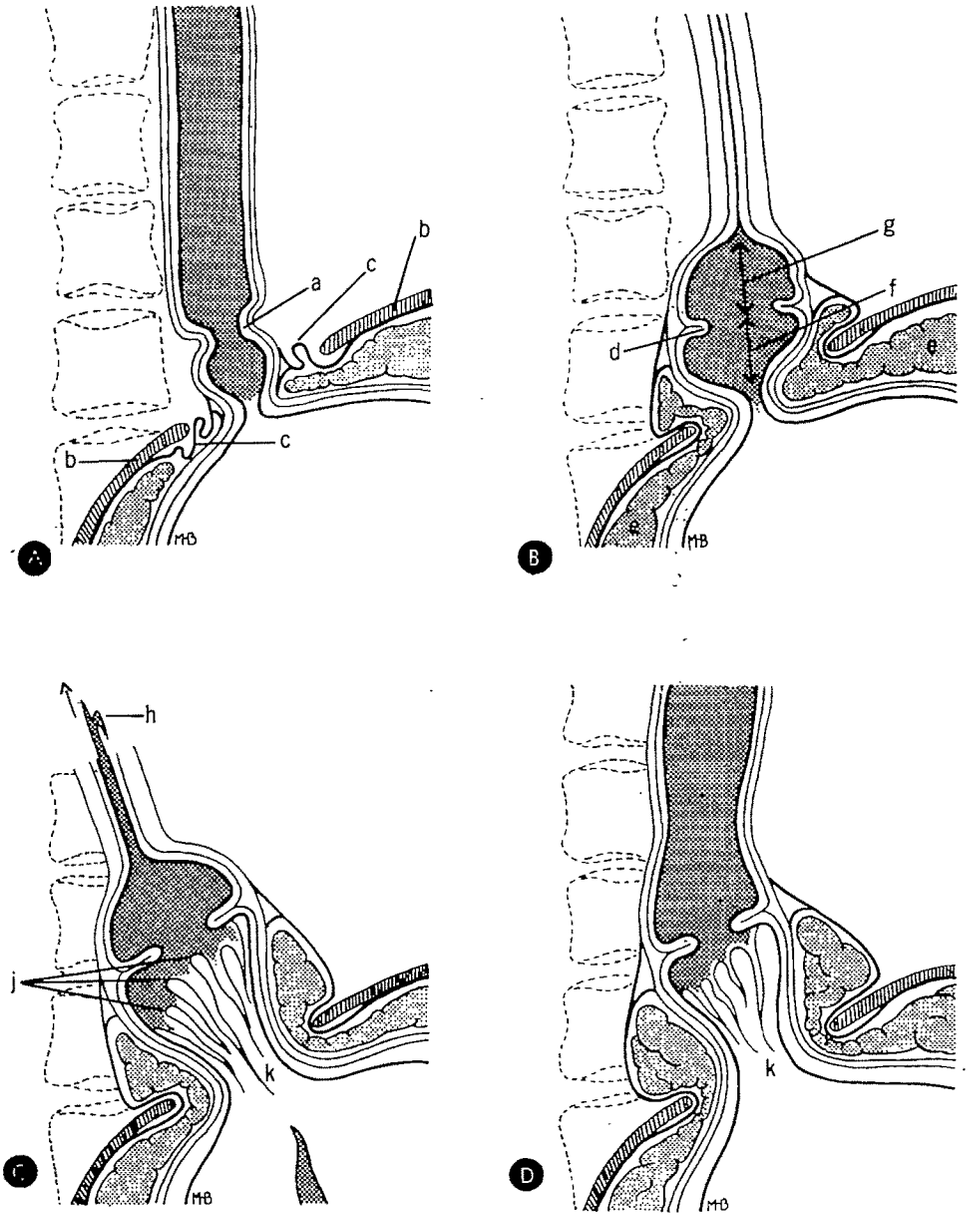


FIG. 2. (*A*) The patient is swallowing barium in the normal fashion. The sphincter (a) is situated 1 to 2 cm. above the diaphragm (b). The phrenoesophageal ligament (c) is slack.

(*B*) When the patient strains, the longitudinal muscle of the esophagus contracts, the phrenoesophageal ligament is retracted above the diaphragm and forms a tent-like enclosure. The esophageal mucosa becomes redundant and forms a web or ring (d). Intra-abdominal pressure forces loosely attached structures near the hiatus (e) into the tent of the phrenoesophageal ligament, distending it and at the same time compressing the "herniated" segment of the stomach (f). Meanwhile a peristaltic wave has formed, progressing as far as is possible distally in the esophagus and terminating at the lower margin of the physiologic sphincter which remains closed. The barium trapped between the pinchcock at the diaphragm and the physiologic sphincter is the "captive bolus." The zone (g) below the lower margin of the physiologic sphincter and above the web represents a region having unique physiologic properties. See text.

(*C*) As the maximal straining effort of the Valsalva maneuver is sustained, the physiologic sphincter is unable to withstand the hydrostatic pressure generated by further encroachment of the abdominal structures into the phrenoesophageal tent. This results in proximal ejection of a jet (h) from the captured bolus.

tudinal muscle of the esophagus is not contracted. This can be verified by a simple clinical experiment.

The best subject for this experiment must have clear-cut symptoms of pyrosis, acid regurgitation, etc., and a negative response to the "captive bolus test." He must either be capable of belching on command or (more commonly) be able to make effective efforts at eructation. The initial maneuver of a spontaneous or controlled belch is a modified Valsalva maneuver. This maneuver *per se* is capable of causing reflex contraction of the longitudinal muscle although in practice it is difficult to separate the effects of this contraction from the concurrent rise in intra-abdominal pressure. It is for this reason that it has been the weight of opinion for many years that increased intra-abdominal pressure is the cause of hiatus hernias despite the early speculations of von Bergmann and Goldner[22] and the experimental work of Dey, Gilbert, Trump and Roskelley.[6]

In a high proportion of this rather limited group of patients, the attempt to belch will almost instantly result in the production of a hiatus hernia. If the patient is then asked to perform a sustained Valsalva maneuver, a typical captive bolus and hydraulic pump can be demonstrated.

This experiment suggests that contraction of the longitudinal muscle and, as a result, elevation of the phrenoesophageal ligament are necessary for the formation of the pinchcock and associated mechanisms. As a byproduct, it chances that these considerations put a rational theoretic foundation under the Nissen[16] and Boerema[4] operations. By fixation of the esophagus via the lesser curvature of the stomach, these procedures prevent the esophagus from shortening when the longitudinal muscle contracts; the tent cannot form

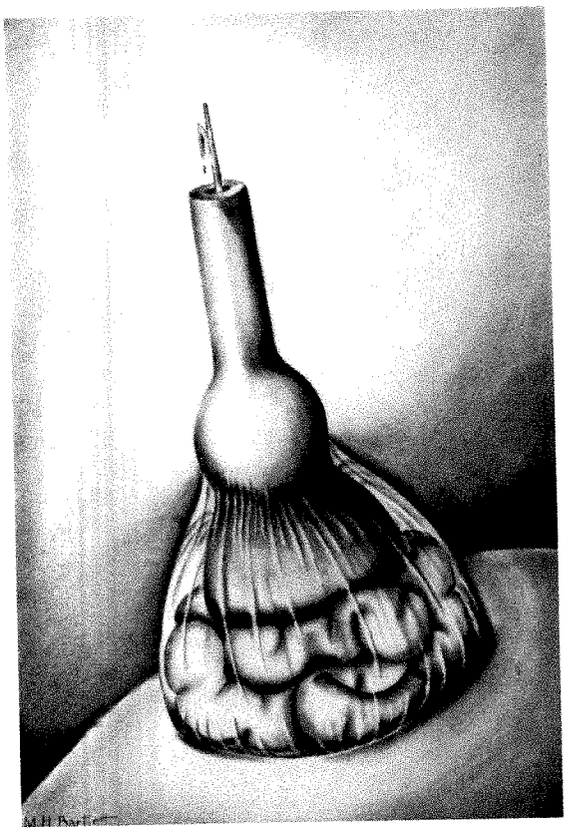


Fig. 3. From this artist's reconstruction of the processes detailed in Figure 2, *A–D*, the operation of the pump mechanism can be seen at a glance.

As the mucosal surfaces of the tubular segment of the stomach are forced together (j), the illusion of "retrograde prolapse" of gastric mucosa is created.

(*D*) Finally, nearly all of the gastric tube is collapsed by encroachment of the abdominal stuctures into the phrenoesophageal tent. The physiologic sphincter yields completely, but the pinchcock (k) remains tightly closed. The captive bolus is ejected into the esophagus. It may be milked back by the next peristaltic wave and the cycles shown in *A* through *D* are repeated two or more times. The collapse of the gastric segment is often symmetric at first, but at its end-point may be quite asymmetric, closing anteriorly while there is still a pocket of barium posteromedially. The complete collapse of the herniated stomach in conjunction with the redundant mucosa of the lower esophageal ring produces the "wing" sign. The "arum lily"[1] appearance, sometimes labeled "transmigration of esophageal mucosa," occurs as the elasticity of the phrenoesophageal ligament attempts to crowd the contents of the tent back toward the abdomen.

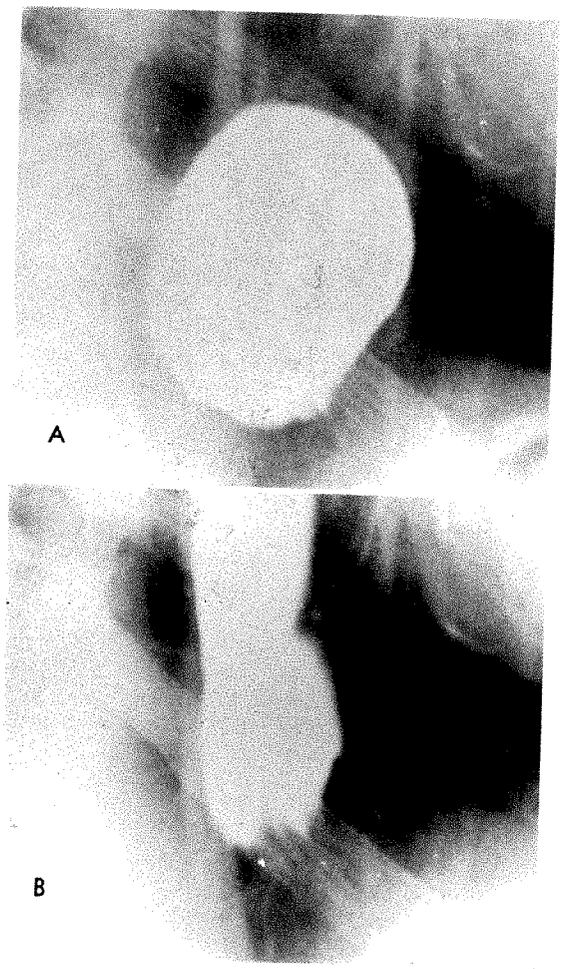


FIG. 4. These underexposed roentgenograms were made to show the soft tissue envelopment of the pinchcock above the diaphragm. (*A*) The captive bolus. (*B*) The "empty segment." In each case the phrenoesophageal ligament is retracted above the hiatus by traction of the longitudinal muscle of the esophagus. As abdominal contents crowd into the "tent," they collapse the portion of the fundus as in (*A*) to form a pinchcock and eventually force barium into the body of the esophagus to form an "empty segment" as in (*B*). Note the triangular radiolucency between the tent and the heart outline.

(indeed, with vigorous downward traction the cone is inverted) and the hernia, etc., cannot form. The frequent failure to redemonstrate hiatus hernia in patients under ulcer management is also understandable in these terms as these patients are receiving anticholinergic drugs which may reduce the tone of the longitudinal muscle. The implications with respect to the cause of hiatus hernia are readily apparent.

If a patient swallows a large bolus or swallows continuously, even though a pinchcock action is set up, there will be no captive bolus. This is due to the fact that peristaltic waves die out and reform if they are not able to bring the esophageal walls into contact. In a patient with a long phrenoesophageal ligament and a highly competent pinchcock, a sufficiently powerful peristaltic wave cannot form for the same reason. It is important, therefore, to give only a moderate sized swallow of barium so that good peristaltic waves can form and force the pinchcock to the limit of their travel.

DIRECT DEMONSTRATIONS OF THE PHRENOESOPHAGEAL TENT

An obvious objection to the "pinchcock pump" mechanism is the fact that no tent-like projection above the diaphragm has been described although there has been ample reason to search for it on other grounds. Certainly, one's attention is distracted from soft tissue shadows in the retrocardiac region by the already complicated relationships he is attempting to observe in the barium filled esophagus and stomach. It seemed that such a tent might have been simply overlooked. A careful search for this structure on roentgenograms made with a photo-timed spot film device was unsuccessful. It was only when we began using "hand-timed" spot films that this structure came to light. Its demonstration is usually far from ideal and very light spot films must be obtained (Fig. 4, *A* and *B*). The heart obscures the outlines of the phrenoesophageal tent anteriorly and the descending aorta and other paravertebral shadows tend to obscure it posteromedially. Moreover, the higher right leaf of the diaphragm envelops and obscures the entire region. Nevertheless, on suitable films one can reconstruct the tent by following the pleuroesophageal stripe down to the region of the lower esophageal ring where it

suddenly becomes 3 or 4 times its normal width and then diverges sharply from the outline of the pinched-off stomach. Anteriorly, a vague radiolucent area can be seen between the heart shadow and the poorly defined margin of the tent. Oddly enough, due to some accident of the engraving process, it can often be seen in published cases of hiatus hernia. Occasionally, it may be seen as clearly as in Figure 4, *A* and *B* when the patient is emphysematous and the right leaf of the diaphragm is depressed below the level of the left.

The elusiveness of the tent may well provide the explanation for its contents, suggesting that fatty tissues occupy the potential space when intra-abdominal pressure forces abdominal contents into the cone.

Closely adjacent to the hiatus are the gastrohepatic omentum, the left lobe of the liver, regional lymph nodes, blood vessels and lymph vessels and even the gastrolineal ligament, any of which structures could form the actual physical content of the sac. Considering the tremendous incidence of hiatus hernias, and the fact that with a small hiatus and a long phrenoesophageal ligament there is ample opportunity for incarceration of adjacent structures, it would be very strange if such incarcerations did not occasionally occur, although I know of no such cases at the moment.

"ELEVATOR" ESOPHAGUS

Just as reconstruction of the dynamics which enable a bolus to be captured leads to an explanation for the diaphragmatic pinchcock, the latter leads to a simple account of other phenomena which have been inexplicable or poorly understood. The striking effect Dreyfuss and Willocx[8] described as "elevator esophagus" and Evans[9] as "a peculiar dysrhythmia" is a remarkable phenomenon sometimes observed in a patient in the upright position, especially if he has swallowed air along with the barium. A fluid level forms at the air-fluid interface which ascends and descends in the fashion of an erratic elevator. This can be due to either (1) inhibition of peristalsis by an overfilled esophagus with a highly effective pinchcock in which case peristaltic waves form and narrow the esophagus, causing a rise in the fluid level, and then die out, causing the fluid level to descend, or (2) to alternate episodes of reverse ejection of barium from the captive bolus by the cardiac pump and downward milking of the column by effective peristaltic waves.

RETROGRADE PROLAPSE OF GASTRIC MUCOSA

Study of cine-films of the captive bolus as it is being ejected proximally shows that the lower margin of the bolus assumes a progressively more concave appearance at a progressively higher level. As one sees the gastric mucosa only where the walls of the gastric tube are forced together by the pinchcock and as the advancing edge of the pinchcock is moving proximally, the illusion that the mucosa itself is herniating proximally into a tubular esophagus is produced. A dozen or so articles in the literature[10,11] testify to the frequency with which this has been observed in recent years. I doubt that any of the cases reported under this heading represent true retrograde prolapse.

ORTHOGRADE PROLAPSE OF THE ESOPHAGEAL MUCOSA

Aldridge[1] has recently reviewed this subject, preferring the less committal term "transmigration of the esophageal mucosa." Characteristic of the "condition" is a configuration which Aldridge likens to the appearance of an arum lily. This appearance is seen as the hernia provoked by the Valsalva maneuver reduces at the end of the test. The longitudinal muscle relaxes and the esophageal length is returned to normal. At the same time, the herniated stomach attempts to slide back into the abdomen through the still prolapsed cuff of abdominal contents which are also crowded through the hiatus. Its upper portion "overflows" the opening and is plowed up against the side of the esophagus, producing

a distortion of the former which causes this "Jack-in-the-Pulpit" or "arum lily" appearance. When a lower esophageal ring is present, its free edges form the upper portion of the "stamen." The "Saturn ring" sign and the "wing sign" are also produced by this sliding down of the herniated segment of the stomach. In a single cine-strip one may see in succession the "Saturn ring"—due to a pinching off of the circumference of the gastric tube as it begins to reduce—the "Jack-in-the-Pulpit" sign and finally the "wing sign" due to the aperistaltic segment flattened between the lower esophageal ring and the sphincter by the pinchcock pump.

These slight gastrogastric and esophagogastric invaginations occur with great regularity and have, I believe, been a source of much misunderstanding.

The difficulty arises if one applies reasoning which is perfectly correct for an Akerlund Type III hernia to a Type I. That is, in the former it is the weight of the stomach which is the restorative force—easily demonstrated by tilting the patient erect. In the sliding hernia (Type I) *it is the elasticity of the phrenoesophageal ligament which provides the restorative force.* As Hayward[12] has emphasized, this membrane is an exceedingly elastic structure "rich in elastic fibers" which "if . . . divided near the esophagus . . . may be taken right up into the adventitia of the esophagus and vanish." Moreover, this force is applied at the *apex* of the gastric tube not at its hiatal margin. Thus, there is a tendency to telescoping if the herniated stomach cannot slide through the hiatus as fast as the ligament retracts.

These configurations represent cross sections of the process of herniation-reduction and should not be dignified as diseases in their own right.

THE PHRENIC AMPULLA

Some years ago an astute clinician requested that I report it when I found phrenic ampulla in his patients, explaining that as he was unable to distinguish clinically between the symptoms of hiatus hernia and those encountered in patients who had well marked phrenic ampullas, he was convinced that the latter were symptomatic.

As it is impossible to get sufficient distention of the terminal esophagus to produce the inverted turnip shape we know as a "phrenic ampulla" without a diaphragmatic pinchcock and as the latter cannot form unless there is elongation of the phrenoesophageal ligament, it follows that demonstration of the turnip implies elongation—*i.e.*, hiatus hernia. Further, our analysis (Fig. 2*B*) indicates that all but 1 to 3 cm. of this structure is gastric. What then becomes of the phrenic ampulla?

It seems impossible to avoid the conclusion that except for the short region described below it is largely a nonexistent structure and that what we have been labeling "phrenic ampullas" are actually small "hiatus hernias" which we have been unable to identify as such for lack of landmarks. When a ring is seen in such patients, it provides a landmark which permits positive identification of the esophagogastric junction (Fig. 2*B*), confirming the above analysis.

THE ZONE OF WEAK OR ABSENT PERISTALSIS

A careful study of cine-films of the captive bolus test reveals a short terminal segment of the distal esophagus to have distinctly different physiologic properties. This zone is bounded above by the lower margin of the sphincter. Its inferior boundary is usually identified by the lower esophageal ring, which, although not always present as a well developed structure, can usually be identified on a few frames as two slight notches in the barium column, corresponding perfectly with the notches described by MacLean[14] and others and identified by Zaino, Poppel, Jacobson, Lepow and Osturk[23] as the mucosal junction. As the peristaltic wave milks the barium column into the terminal esophagus and herni-

ated segment of the stomach, it *never* advances beyond the inferior margin of the sphincter. Moreover, the aperistaltic segment is more distensible than the esophagus above it, or at least distends more as it has to withstand the considerable pressure generated by the pump mechanism. Because of this distensibility, its girth matches that of the herniated gastric tube. It is for this reason that, lacking a ring, the early observers in describing a phrenic ampulla were including a large gastric segment in their definition of that structure, unaware that most of the "phrenic ampulla" was herniated stomach.

Apart from the somewhat artificial conditions of the test, the aperistaltic zone can be identified as an air filled cone at and a centimeter or so above the diaphragm when a patient attempts to belch or with straining when the esophagus is empty. Certainly, there is some muscular contraction here as the zone can be seen opening and closing repeatedly in some patients, especially preparatory to a belch. When it does open, it appears as a conical tube under tension. This fact can be taken as a further clue that the initial impulse to opening of the inferior sphincter of the esophagus is a contraction of the longitudinal muscle.

Despite its existence, there seems to have been no clue to the aperistaltic segment in manometric studies. These locate the physiologic sphincter at the point of inspiratory pressure reversal. Hence, the aperistaltic zone must have manometric characteristics of fundic stomach—justifying my somewhat tentative description of the region as "aperistaltic."

CARDIOESOPHAGEAL REFLUX

Although we have at hand a mechanism for ejecting the gastric contents into the esophagus under considerable pressure and with great effectiveness, and there seems to be little doubt that under certain circumstances this mechanism does actually do so, it is not a complete explanation of the cause of cardioesophageal reflux. Numerous additional factors have to be taken into account. The test is essentially unphysiologic and encountered in daily life chiefly with straining or belching.

HIATUS HERNIA

It can be seen that, strictly speaking, the presence of a "captive bolus" is actually an indication of hiatus hernia. I would rather not put it just that way, however, as this leads inevitably to conclusions which are either startling or ridiculous, depending on viewpoint. Series have been reported in which the incidence of hiatus hernia has been as high as 50 per cent (Stein and Finkelstein[18]). If a series were collected employing the usual tests for hiatus hernia and in addition the "captive bolus" test, to the hiatus hernia category would be added all those cases with a "captive bolus" or "phrenic ampulla," perhaps raising the percentage into the 70's or 80's. When the incidence of a condition is this high, the examiner is in the paradoxical position of wishing he had less rather than more sensitive tests. Some authors have actually deliberately chosen less sensitive tests in conducting studies of hiatus hernia.[21] I would be in favor of employing the most sensitive tests possible and letting the chips fall where they may, that is, leave it to the clinician to decide which hernias are significant. This is actually not difficult to do as the symptom of acid reflux is a nearly infallible indication of sphincter incompetence and the test of Bernstein *et al.*[2,15] is readily available as a check if the symptoms are atypical. Moreover, there are other roentgenologic studies of the cardiac mechanism available on which to base an opinion as to the significance of the "hernia". The problem is actually a semantic one which we might choose to avoid by simply labeling the syndrome "relaxation of the phrenoesophageal ligament."

SUMMARY

A simple new procedure, the "captive bolus" test, is described. This test gives a

measure of the length of the phrenoesophageal ligament and leads to explanations of the "wing" and "Saturn ring" signs. It also indicates that most, if not all, reported cases of "orthograde prolapse of the esophageal mucosa" and "retrograde prolapse of the gastric mucosa" are spurious. The cause of the pinchcock at the diaphragm is explored and the existence of a hitherto undescribed hydraulically actuated, retrograde pump at the cardia is described and analyzed. This pump may be of significance in accounting for pyrosis in certain cases of hiatus hernia.

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LOCALIZATION OF PARATHYROID ADENOMAS BY ESOPHAGEAL CINE-ROENTGENOGRAPHY*

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OUR experience in 4 families[5] (25 individuals) with hyperparathyroidism and that in cases detected by a routine serum calcium screening survey[1,2] (31 affected in 26,000 consecutive individuals) has emphasized the occasional usefulness of ordinary roentgenography of the cervical esophagus in locating parathyroid adenomas. However, the defect may be only fleetingly observed and is often difficult to capture on spot roentgenograms. The possibility that cine-esophagraphy[9] might obviate these difficulties occurred to us and the 11 patients reported here were studied by this technique prior to neck exploration.

METHODS

Patients with hyperparathyroidism as determined by clinical and laboratory studies were referred for possible localization of the parathyroid adenoma by cine-roentgenographic studies of the esophagus. Only patients who have had subsequent neck explorations are included.

Cine-esophagraphy was performed, using barium of the same consistency as is used normally for upper gastrointestinal fluoroscopy. Films were exposed with a 35 millimeter camera at 15 frames per second. By using several barium swallows, the size of the bolus tended to vary, allowing examination of the esophagus in several states of distention.

ROENTGEN ANATOMY

Figure 1, modified from Gilmour,[4] illustrates the most common positions in which the parathyroid glands may be found in relation to the thyroid gland and adjacent structures in the neck. The esophagus begins at the inferior border of the cricoid cartilage at the level of C6 where there is evidence of a constriction. The spinous processes of the vertebral bodies serve as excellent and accurate markers of the midline.

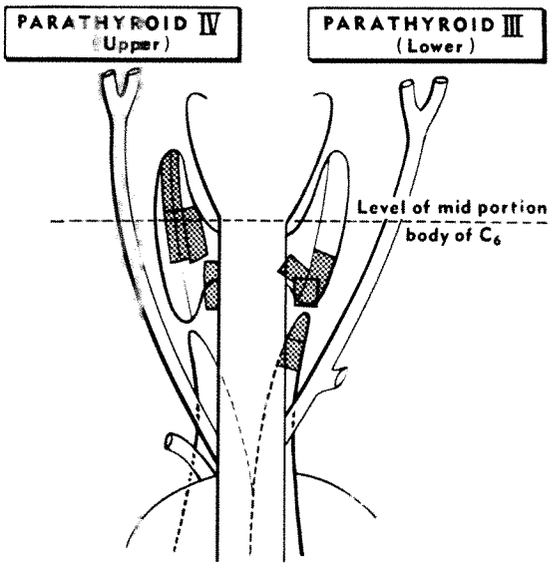


FIG. 1. Stippled areas represent most common location of normal parathyroid glands. Note position of parathyroids III at upper pole of thymus gland. Modified from Gilmour.[4]

Normally, the pharyngo-esophageal angles are obtuse and symmetric bilaterally. The most proximal esophagus is in the midline and distends almost equally on both sides with the barium bolus. The lower cervical esophagus deviates gradually and slightly to the left. As the most proximal portion of the esophagus is studied frame by frame throughout the entire passage of the bolus, no notches or indentations are present normally.

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TABLE I

CINE-ESOPHAGRAPHIC FINDINGS

Patient	Age and Sex	Pre-Surgery Serum Calcium Range (mg. %)	Asymmetry in Pharyngeal-Esophageal Angle	Deviations of Esophagus	Defect	Surgical and Pathologic Findings
1. B. L.	54 M	10.9–11.9	rt. straightened	no	rt. at C7–D1	right upper parathyroid adenoma, 2.4×1.4×1 cm.
2. C.A.	56 M	10.2–11.4	no	no	rt. at C6–C7	left upper parathyroid adenoma, 2.3×1×.8 cm. (0.89 gm.); right upper thyroid nodule
3. J.S.	46 M	10.8–12.2	rt. straightened	to left at D2–D3	lt. at C7–D1	left upper parathyroid adenoma, 1.7×.9×.8 cm. (0.53 gm.); left lower thyroid nodule
4. A.S.	53 F	14.7–14.8	rt. straightened	no	rt. at C7–D1	right lower parathyroid adenoma 2.5×1.9×1.5 cm. (1.9 gm.)
5. G.W.	55 F	10.9–11.8	lt. straightened	to right	lt. at C7–D1	left lower parathyroid adenoma, 2.5×1.2×.5 cm. (0.95 gm.); enlarged thyroid, thyroiditis
6. M.G.	48 F	10.1–12.3	rt. straightened	no	rt. at C7	right upper parathyroid adenoma, 2.4×2.4×1.8 cm. (3.9 gm.); nodular thyroid
7. F.R.	74 F	10.2–11.3	no	to left	rt. at C7–D1	right lower parathyroid adenoma, 1.0×.7×.5 cm. (0.15 gm.); enlarged nodular thyroid
8. G.M.	48 F	9.6–10.9	no	no	rt. at D1	right lower parathyroid adenoma, 1.7×1.2×.8 cm. (1.1 gm.)
9. G.L.	61 M	11.3–12.9	lt. straightened	to left	rt. at D2	right upper parathyroid adenoma, 2.2×1.9×1.6 cm. (4.4 gm.)
10. O.Y.	61 F	10.3–11.7	defect in rt. angle	no	rt. at C6–C7	left lower parathyroid adenoma, 1.4×.9×.6 cm. (0.44 gm.); right lower thyroid nodule
11. R.F.	62 F	10.4–11.2	lt. straightened	to right	lt. at C7–D1	right lower parathyroid adenoma, 1.8×.9×.4 cm. (0.43 gm.); left lower thyroid nodule



FIG. 2. Case 1. Right pharyngo-esophageal angle is straightened. Triangular defect of right esophageal wall peaking at level of C7–D1 interspace. Parathyroid adenoma, 2.4 cm.×1.4 cm.×1 cm. of right upper pole.

RESULTS

Table 1 is a summary of the clinical, cineroentgenographic, surgical and pathologic findings in the 11 cases studied. Figures 2 through 5 are cine-esophagrams of selected patients. It may be observed that the parathyroid adenoma was correctly localized in 5 of the 11 cases (Cases 4, 5, 6, 7 and 8). The incorrect localization in 3 cases (Cases 2, 3 and 11) can be attributed to the presence of thyroid nodules. In 2 patients (Cases 1 and 9), the side but not the level was localized correctly.

DISCUSSION

In 1954, Wyman and Robbins[10] published a comprehensive study describing the roentgen localization of parathyroid adenomas by ordinary esophageal fluoroscopy and filming. Many of their patients had

large tumors with unmistakable gross esophageal displacement and indentations. Little emphasis has been placed heretofore on the localizing of parathyroid adenomas by cine-roentgenography except incidentally in a study by Scatliff and Scibetta[8] in which the changes are described in 2 cases of parathyroid adenomas.

The 3 main signs suggesting the presence and position of a mass lesion, whether thyroid or parathyroid, are: the shape of the pharyngo-esophageal angle, deviation of the esophagus, and defects in the esophageal walls. A fourth finding, which is less readily demonstrated, is the loss of the normal pliability and distensibility of the wall of the esophagus.

The configuration of the pharyngo-esophageal angle often serves as a good indication of the side of involvement, even when the mass lesion is a relatively small nodule located at the lower poles (Cases 1, 4, 5, 6 and 11).

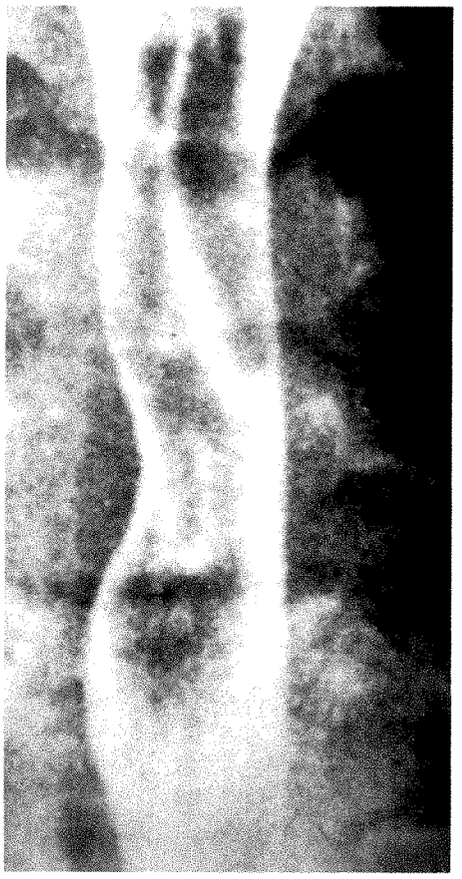


Fig. 3. Case 8. Prominent crescentic defect in the right esophageal wall at the level of D1. Parathyroid adenoma, 1.1 gm., of right lower pole.

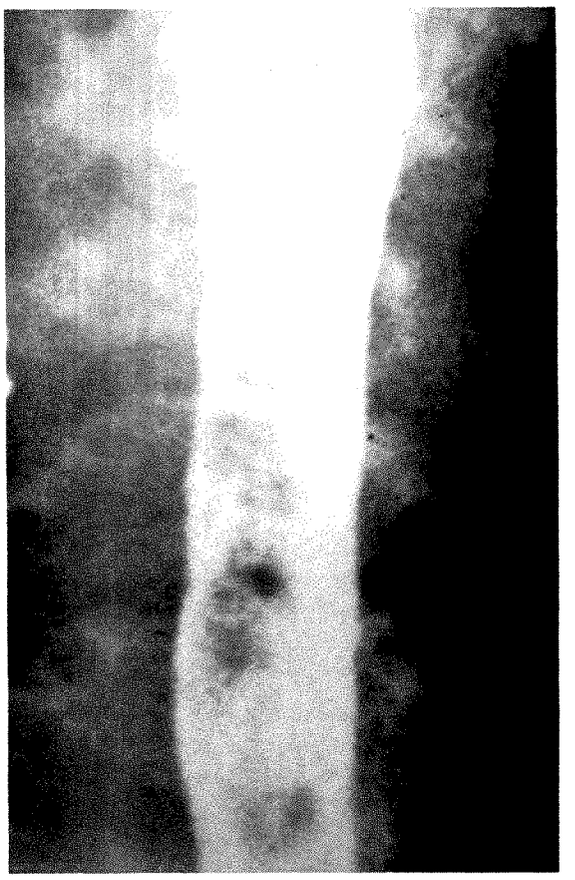


Fig. 4. Case 8. Postoperative cine-esophagram. Complete disappearance of the defect.

Displacement of the esophagus was caused by enlargement of a portion of the thyroid gland (Cases 5, 7 and 11). In this study, esophageal displacement was not seen without enlargement of the thyroid except in Case 9 (Fig. 5) which had a very large parathyroid adenoma.

Defects in the esophageal walls, although occasionally small and fleeting, proved to be the most important of all the signs. These defects (except in Case 10) were produced by adenomas (7 parathyroid and 3 thyroid). In Cases 1 and 9 (Fig. 2 and 5) the adenoma was at the upper pole but the defect was noted at a level which would

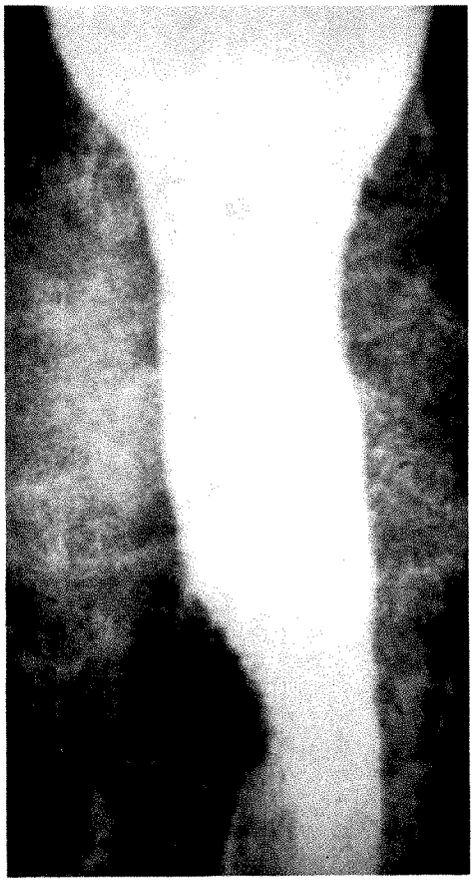


FIG. 5. Case 9. Slight straightening of the left pharyngo-esophageal angle with deviation of the esophagus to the left. Large defect in the right esophageal wall at the level of D2. Parathyroid adenoma, 4.4 gm., of right upper pole.

suggest a lower pole lesion—possibly due to a movement of the fairly large adenoma to a lower level in the erect position.

Defects located at the level of the C6–C7 interspace or upper part of the body of C7 vertebra suggest a nodule at the upper pole of the thyroid gland (Cases 2, 6 and 10)—those situated at the level of the lower part of body of C7 or D1 or at this interspace suggest a lower pole mass (Cases 1, 3, 4, 5, 7, 8, 9 and 11). The incorrect findings in Case 10 remain unexplained although thyroid nodules were noted at surgery but not in the location suggested.

Several investigators have utilized radioisotopic techniques[3,7] and pneumomediastinum[9] for localizing parathyroid adenomas. Cine-roentgenography seems to be considerably simpler and this initial experience suggests a rather high degree of accuracy even in cases of small adenomas.

SUMMARY

Although ordinary roentgenography of the esophagus is occasionally helpful in localizing parathyroid adenomas prior to surgery, the defect is often fleetingly observed and difficult to capture on spot roentgenograms. To investigate the possibility that cine-esophagraphy might obviate these difficulties, 11 patients were studied prior to neck exploration. In 5 patients, the adenomas were correctly localized. In 2 instances, the side suggested was correct but the adenoma involved the upper gland rather than the lower gland suggested by the defect on the esophagram. The incorrect localization in 4 cases was associated with the presence of thyroid nodules. It is our opinion that cine-roentgenography of the cervical esophagus provides a relatively simple and often fruitful method for the preoperative localization of parathyroid adenomas.

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A NEW TECHNIQUE OF CONTRAST EXAMINATION OF THE NASOPHARYNX WITH CINEFLUOROGRAPHY AND ROENTGENOGRAPHY*

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HISTORICAL SURVEY

THE value of the plain roentgenographic examination of the nasopharynx, with particular reference to the detection of tumors, has been increasingly recognized since the third decade of this century, and outstanding contributors included Mayer[7] and Pfahler.[8]

Contrast study of the nasopharynx soon followed. Groth,[3] in his article, points out that in 1931 Zuppinger described a method of lateral roentgenography of the nasopharynx with the patient's head hanging down following the introduction of lipiodol. Both of these authors were interested in the demonstration of adenoids in children with contrast roentgenography.

Welin,[13] in 1952, advocated contrast roentgenography of the nasopharynx with the patient in the dorsal decubitus position, following which lateral and axial exposures are made. In his opinion, contrast roentgenography does not provide any added information in comparison with the less innocuous plain roentgenographic examination of the nasopharynx.

In the same year, Samuel[11] described in detail the method of contrast roentgenography of the nasopharynx used by Rüedi and Zuppinger in 1934. Lipiodol was instilled into the nostrils with the patient recumbent, followed by lateral roentgenography of the nasopharynx half a minute later. Subsequently, in 1954,[12] he described a technique in which lipiodol was instilled into the nose and allowed to flow over the nasopharynx. Roentgenographic examination was then performed in the lateral and submentovertical planes. Samuel doubted that the additional information gained by contrast study was worthwhile in comparison to the more accurate, though uncomfortable, procedure of direct pharyngoscopy.

Baclesse[2] in 1956 stated that roentgenologic study of the nasopharynx was facilitated by "thin layer" opacification. His patient was placed in the dorsal decubitus position, with head in extension. An ordinary syringe was used to inject 1 or 2 ml. of lipiodol into the nostril, and profile roentgenograms were taken at once. Excellent lateral contrast roentgenograms of the nasopharynx, supplied by Baclesse, can be seen in the monograph of Maduro and Bouche[6] on diseases of the pharynx.

In his monograph on cancer of the nasopharynx, Lederman[5] describes the use of barium for contrast roentgenography and says that this technique is of value for the detection of nasopharyngeal tumors. Ho[4] currently stated that he preferred roentgenography of the nasopharynx without the use of opaque medium. In fact, he feels that contrast medium is contraindicated as it obscures underlying bone structures.

At this point, it may be noted that there was more interest in contrast roentgenography of the paranasal sinuses in the earlier days, beginning at the start of this century, than there is today. This culminated in the displacement method of sinus diagnosis and treatment by Proetz[9] before 1930. According to Proetz, Fraser in 1927 gave credit for this method to Moritz Weil, who in 1902–1903 used aqueous mixtures of lead sulfate for visualization of the maxillary and frontal sinuses.

COMMENT

From the foregoing account, it can be gathered that Zuppinger in 1931 was prob-

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ably one of the earliest investigators to report on contrast roentgenography of the nasopharynx. Others included Groth[3] in 1933 and Rüedi and Zuppinger in 1934. Relatively little had been published until over two decades later, and except for Baclesse[2] most contemporary authorities appear to have had little enthusiasm for this method of study.[4,11,12]

Only lateral contrast roentgenograms were taken in the early days, but, subsequently, the axial or submentovertical projection was added. The contrast substance used was either lipiodol or barium sulfate, instilled directly into the nose with the patient recumbent and head extended. Roentgenograms were taken immediately or soon after instillation of contrast medium.

Although all investigators appeared to have limited themselves only to the lateral and submentovertical positions for visualization of the contrast filled nasopharynx, one of us (F.Y.K.) felt that there might be a place and use for visualization of the contrast filled nasopharynx in the frontal (posteroanterior or anteroposterior) position. A search through relevant roentgenologic and ear, nose and throat textbooks on the nasopharynx failed to disclose that a frontal projection had ever been described. This apparent lack of interest might be attributed to the following factors: (a) the study of the nasopharynx is not widespread and has so far been confined to workers interested in cancer work; (b) the lateral and submentovertical projections appeared to suffice for practical purposes; besides, most investigators felt that not much more information could be gained when compared with plain roentgenography; and (c) there is no suitable technique of satisfactorily filling the nasopharynx with contrast substance under visual control for obtaining suitable roentgenograms, much in the same manner as fluoroscopic visualization is needed for suitable spot roentgenograms in a barium meal examination.

Therefore, it would appear to us that a workable technique of contrast roentgenography of the nasopharynx could be developed provided the following three conditions could be fulfilled: (a) the procedure must be relatively innocuous and capable of being tolerated by the patient; (b) availability of a suitable contrast medium providing good contrast as well as good mucosal adhesive property and barium column cohesive power; and (c) roentgen-ray equipment capable of providing convenient fluoroscopy, roentgenography and cinefluorography; the obvious needs are not only a modern image intensification-television set-up, but also development of a roentgenographic technique which can ensure successful cinefluorography.

In August, 1964, the operation of a General Electric Fluoricon unit with provisions for image intensification, television viewing, 16 mm. cinefluorography and a spot-filming device provided us with the essential physical roentgenographic set-up and so enabled us to commence developing a practicable method of visualization of the contrast filled nasopharynx in the frontal projection.

Description of Steps Leading to the Establishment and Standardization of Our Technique of Contrast Roentgenography of the Nasopharynx

A. Patients

Adult patients with carcinoma of the nasopharynx were first investigated. Following successful trials, subsequent patients included those with a normal upper respiratory tract.

Anesthesia. It is essential that the nasopharynx be well anesthetized. This is achieved by spraying both nasal fossae and the nasopharynx with 4 per cent lignocaine followed by insertion of cotton pledgets, soaked in lignocaine, into both nasal fossae. These pledgets must be left in position for about half an hour before satisfactory anesthesia is obtained; otherwise, the patient is liable to gag, retch or sneeze during the roentgenographic examination. No ill ef-

fects have been experienced so far from this method of anesthesia.

B. CONTRAST MEDIUM

Many contrast media were tried including iodatol (Glaxo), dionosil, both aqueous and oily (British Drug House), biligrafin (Schering), and barium sulfate. All these media with the exception of barium sulfate were found to be too liquid and, therefore, unsuitable for our purpose.

Micropaque (Damancy), which is finely ground barium sulfate, was found to be most satisfactory for maximum contrast; this is necessary because of the superimposed dense bone shadows around the nasopharynx. Micropaque was also found to be the best for production of a solid cohesive column of contrast substance. However, to achieve the latter, the micropaque must be prepared in a suspended or paste form. Gum of tragacanth was first tried and found inadequate for production of a thick paste. After several trials, the following formula proved to be most suitable:* micropaque, 25 per cent; sodium carboxymethyl cellulose, 1.5 per cent; and water to make up, 100 per cent.

This mixture is in the form of a paste and can be filled into a 20 ml. syringe and injected via a Jacques rubber nasal catheter. It is conceivable that the gélobarine used by Baclesse,[2] or rugar, might be satisfactory, but unfortunately these are not available locally.

C. ROENTGENOGRAPHIC TECHNIQUE

Position of Patient and Method of Instillation of Contrast Substance. Our interest was centered on visualization of the nasopharynx in the frontal view (posteroanterior projection for cinefluorography or spot roentgenography, as the patient has to be examined supine).

The patient lies supine on the roentgenographic table, with his face looking upwards and the orbito-meatal line directed vertically. A Jacques rubber nasal catheter is then introduced through an anterior naris with its tip touching the posterior wall of the nasopharynx; this should be ascertained by viewing the nasopharynx in the lateral position before injection. This is most important to ensure satisfactory filling of the nasopharynx. The patient should be instructed to breathe through the mouth and not to swallow until told to do so.

Barium should be injected under fluoroscopic control. Initially, about 2 ml. of barium suffices for production of a good central column of barium within the nasopharynx (Fig. 1*A*; 3*A*; 6*A*; and 9*A*). This we call the central or "functional" channel of the nasopharynx (for details see under Discussion). Care must be taken not to introduce too much barium at the beginning as any excess may escape into the posterior nasal fossae, thereby partly obscuring the nasopharynx (Fig. 4*A*; and 5*D*).

We find that fluoroscopy of the nasopharynx in the posteroanterior position is satisfactory under the usual conditions of operation of the Fluoricon unit. We find it useful to ask patients to swallow and discover that the nasopharynx is as much a dynamic structure as the lower parts of the pharynx, for it not only possesses tone, but is also capable of actively contracting and expanding during swallowing (Fig. 1, *A–D;* 2, *A–D;* 4, *A–D;* 6, *A–D;* and 7, *A–D*). Swallowing also aids in filling of the pharryngeal recesses, and this must be attempted in every case so that the entire nasopharynx can be visualized (Fig. 5, *A*, *B* and *C*). However, a proper study of the dynamic or functional aspect of the nasopharynx can only be satisfactorily observed with the aid of cinefluorography.

D. CINEFLUOROGRAPHIC TECHNIQUE

Coning of Roentgen-Ray Beam. It was only after several trials before satisfactory cinefluorograms could be obtained. We find that secondary scatter from surrounding bones causes various degrees of undesirable fogging of the cine film, and this must be reduced to a minimum before cinefluoro-

* Formula of Warren Y. M. Tan, Pharmacist, General Hospital. The paste should be prepared the day before use, and if required can be made thicker by the addition of more micropaque.

grams of satisfactory quality and contrast can be secured. This can be achieved by closing the diaphragm of the fluoroscopic tube, permitting only a rectangular field of about 8×12 cm., which is sufficient for visualization of the nasopharynx and oropharynx (Fig. 1, *A–D;* 2, *A–D;* 4 *A–D;* 6, *A–D;* 7, *A–D;* and 8, *A–D*). Lead rubber strips placed on the table under the patient's head will further help reduce secondary scatter.

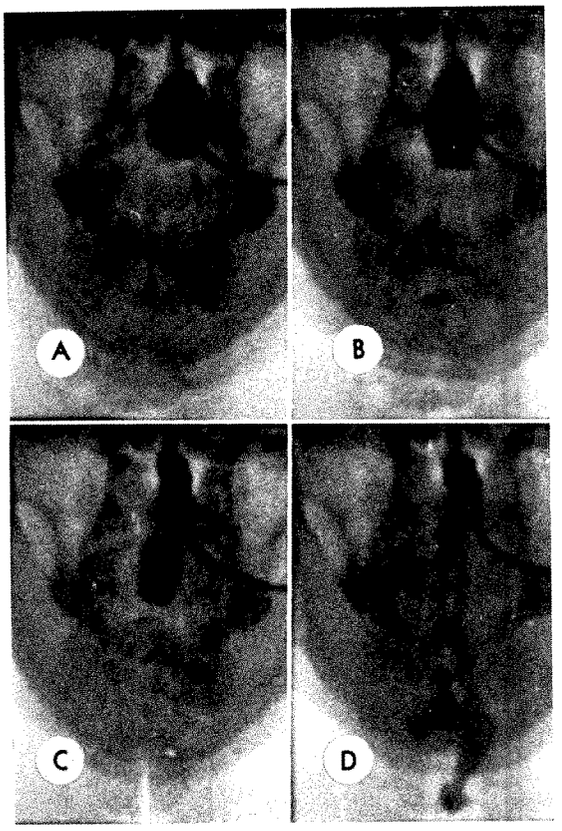


Fig. 1. Case 1. Posteroanterior cinefluorograms of the nasopharynx. (*A*) *Resting phase.* There is homogeneous filling of the lower two-thirds of the nasopharynx with barium, which is thumb-shaped with a convex upper border—the so-called "functional" channel (the high nasopharynx in this patient can best be appreciated in *C*). Note that the lower level of the nasopharynx lies just above the shadows of the upper teeth. The barium filled nasal catheter is seen in all cinefluorograms. (*B*) *Early stage of swallowing.* Some barium is being displaced upwards towards the roof of the nasopharynx. (*C*) *Later stage of swallowing.* The nasopharynx is contracting with moderate narrowing. Note that some barium has been propelled into the high roof of the nasopharynx, carrying the tip of the catheter upwards. This is vividly seen during the cine screening, as the barium column is suddenly shot upwards. Some barium has also descended into the oropharynx. (*D*) *End stage of swallowing.* The nasopharynx is almost emptied of barium except for a blob at its roof, and is narrower than before. Most of the barium is now in the lower pharynx.

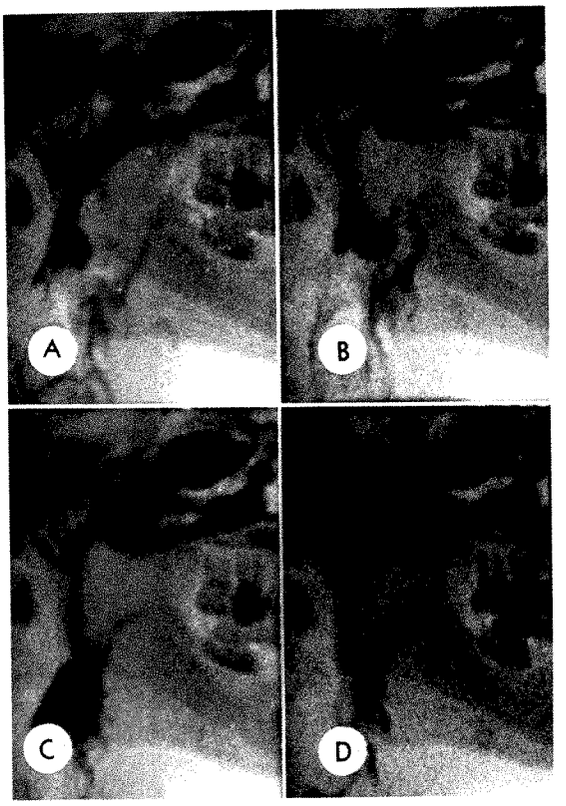


Fig. 2. Case 1. Lateral cinefluorograms. (*A*) Good filling of the nasopharynx with overflow of barium into the nasal fossae. Note good anteroposterior width of nasopharynx. (*B*) Phase of swallowing showing much narrowing of the nasopharynx and elevation of the soft palate. (*C*) Beginning of relaxation of the nasopharynx and descent of soft palate; barium bolus has reached the lower pharynx. (*D*) Nasopharynx relaxed with widening of its anteroposterior diameter.

Choice of Cine Film. Our investigation is based on the 16 mm. cine film. Because of the relatively dense bone parts, high speed, high contrast films should be used. Eastman Tri-X cine film is quite satisfactory (Fig. 6 through 8, inclusive). Kodak Cineflure film gives somewhat better contrast

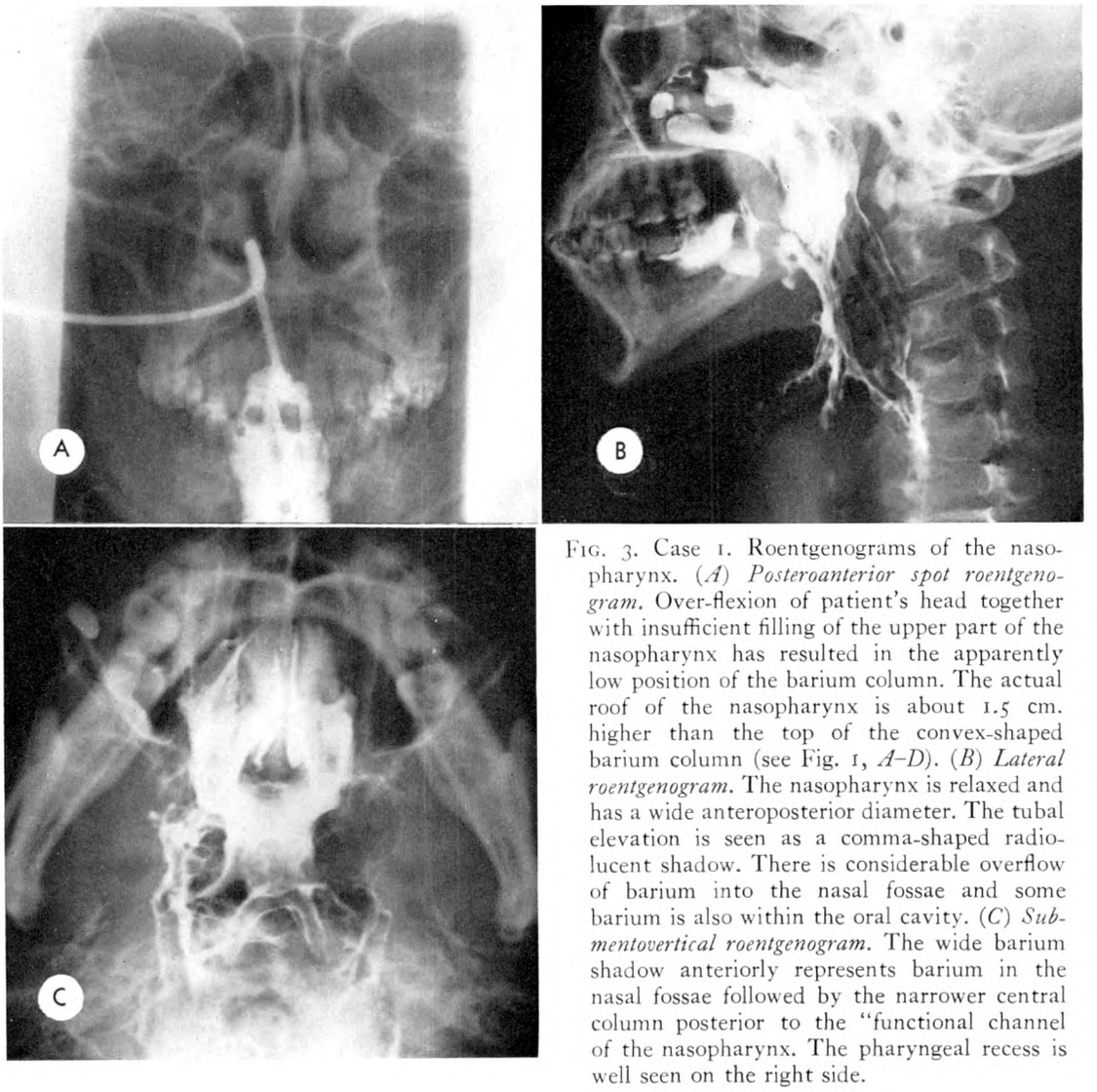


FIG. 3. Case 1. Roentgenograms of the nasopharynx. (*A*) *Posteroanterior spot roentgenogram.* Over-flexion of patient's head together with insufficient filling of the upper part of the nasopharynx has resulted in the apparently low position of the barium column. The actual roof of the nasopharynx is about 1.5 cm. higher than the top of the convex-shaped barium column (see Fig. 1, *A–D*). (*B*) *Lateral roentgenogram.* The nasopharynx is relaxed and has a wide anteroposterior diameter. The tubal elevation is seen as a comma-shaped radiolucent shadow. There is considerable overflow of barium into the nasal fossae and some barium is also within the oral cavity. (*C*) *Submentovertical roentgenogram.* The wide barium shadow anteriorly represents barium in the nasal fossae followed by the narrower central column posterior to the "functional channel of the nasopharynx. The pharyngeal recess is well seen on the right side.

but seems to be of coarser grain (Fig. 1 *A–D;* 2, *A–D*; and 4, *A–D*).

Exposure Factors. We find that films exposed at 30 frames per second are adequate for the study of the dynamic mechanism of the nasopharynx. Because of the dense bone parts, an average kilovoltage range between 90–100 kv. is needed in posteroanterior cinefluorography, using the maximum milliamperage setting available for cinefluorography, under manual control. A useful guide for cine exposure is to add 15 kv. to the appropriate image intensification fluoroscopy kilovoltage.

Others. Besides the frontal projection, cinefluorography including roentgenography in the right and left anterior oblique positions has been found useful (Fig. 5 through 7, inclusive); the patient can then be examined in the lateral position (Fig. 2, *A–D; 3B; 5D;* 8, *A–D;* and 9*C*); and to conclude our routine contrast series a final roentgenogram can be made in the submentovertical position with the patient still on the table (Fig. 3*C;* and 5*E*).

The total amount of barium suspension used is about 20 ml. Our experience has shown that about 20–30 feet of cine film will

suffice for each examination. The total dose of radiation delivered to each patient should be relatively low, considering the small field of exposure, and with the fluoricon image-intensification set-up certainly should not exceed any of the other specialized roentgenographic examinations of the cranium.

REPORT OF CASES

Case I. (Fig. 1 through 3, inclusive). C.F.P., Chinese male, aged 42 years, with suspected peptic ulcer and normal nasopharynx.

On cinefluorograms the lower two-thirds of the nasopharynx was filled in the early stage. The appearance was of a homogeneous thumb-shaped central barium column (Fig. 1*B*) which we call the central or "functional" channel (see under Discussion). On swallowing, part of the barium was forcefully and abruptly shot upwards into the roof of the nasopharynx, which was unusually high in this patient. This upward propulsion proceded the momentary ejection of the main column of barium into the lower portions of the pharynx (Fig. 1, *C* and *D*). The nasopharynx showed considerable power of contraction and relaxation in this patient (Fig. 1, *C* and *D*). In this case the tendency of barium to overflow into the nasal fossae during the later stages of contrast examination was well demonstrated (Fig. 2, *A–D;* and 3, *B* and *C*).

Case II. (Fig. 4 through 5, inclusive). F. P., Indian male, aged 27 years, with suspected peptic ulcer and normal nasopharynx.

Cinefluorograms showed a fairly wide central column of barium within the nasopharynx (the "functional" channel), which later became wider superiorly due to filling of the pharyngeal recesses (Fig. 5, *A*, *B* and *C*). The lower nasopharynx was rather pliable, contracting well and emptying itself almost completely of barium during swallowing (Fig. 4*B*). All oblique projections showed to advantage each pharyngeal recess (fossa of Rosenmüller) with the tubal elevation (torus tubarius) outlined as a triangular radiolucent area within it (Fig. 5, *B* and *C*). The submentovertical roentgenogram (Fig. 5*E*) showed filling of the pharyngeal openings of the auditory (eustachian) tubes and pharyngeal recesses.

Case III. (Fig. 6 through 9, inclusive). C.S.T., Chinese male, aged 53 years, with peptic ulcer and normal nasopharynx.

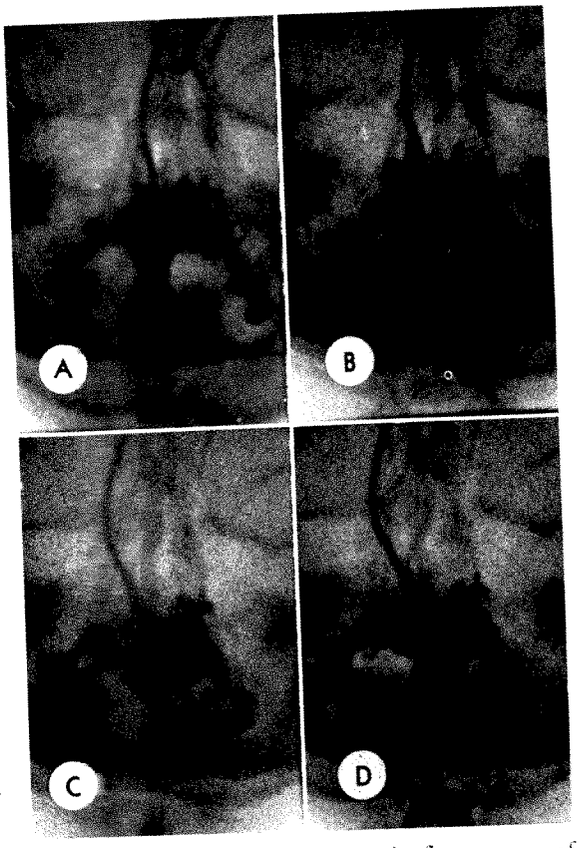


Fig. 4. Case II. Posteroanterior cinefluorograms of the nasopharynx. (*A*) *Stage of beginning of contraction of barium filled nasopharynx during swallowing.* The nasopharynx is fan-shaped superolaterally because of good filling of pharyngeal recesses on both sides, with small streaky shadows superomedially caused by escape of some barium into posterior nasal fossae. The column of barium which is slender in the lower nasopharynx widens into the oropharynx. (*B*) Later stage of swallowing showing good contraction of lower part of the nasopharynx with the barium bolus descending into the lower oropharynx. The pharyngeal recesses do not empty completely. (*C*) End phase of swallowing with some refilling of the upper part of the nasopharynx. (*D*) Relaxation is now complete with barium filling the entire lower nasopharynx, which is of wider caliber than seen in *A*.

Cinefluorograms made while the patient's head was rotated obliquely from side to side showed a thumb-shaped central column of barium within the nasopharynx of medium caliber (the "functional" channel), which emptied quite well on swallowing (Fig. 6, *A–D;* and 7, *A–D*). Spot-roentgenograms showed

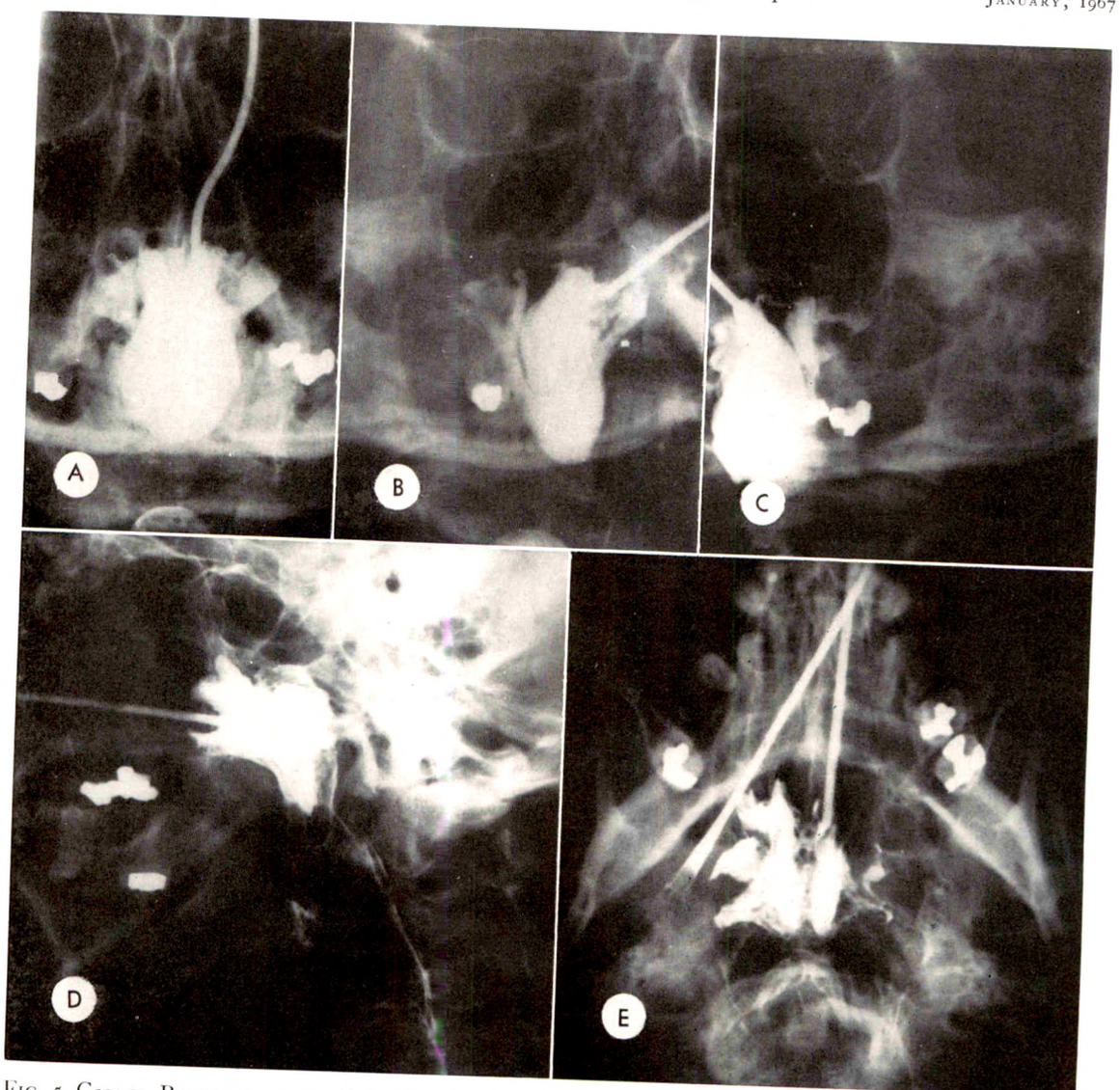


FIG. 5. Case II. Roentgenograms of the nasopharynx. (*A*) *Posteroanterior spot roentgenogram.* Good filling of the nasopharynx. The "functional" channel is seen as a central flask-shaped dense barium column; the less dense upper fan-shaped extensions on both sides represent barium filling the pharyngeal recesses. (*B*) *Right anterior oblique spot roentgenogram.* (*C*) *Left anterior oblique spot roentgenogram.* Both retropharyngeal recesses appear as triangular-shaped extensions superolaterally. The orifice of each pharyngo-tympanic tube appears as an oval radiolucent shadow within each extension. (*D*) *Lateral roentgenogram.* This shows filling of the entire nasopharynx with barium. (*E*) *Submentovertical roentgenogram.* The right pharyngeal recess is well filled and is represented by the posterolateral column of barium on the side of the "functional" channel of the nasopharynx. The comma-shaped barium column in front of the pharyngeal recess represents barium in the pharyngeal opening of the auditory tube.

that the nasopharynx, which at first appeared thumb-shaped with a convex upper border (Fig. 9*A*) became wider and assumed a rectangular shape due to filling of the pharyngeal recesses on both sides (Fig. 9*B*). The lateral cinefluorograms showed complete filling of the nasopharynx with good upward excursion of the soft palate during swallowing (Fig. 8, *A–D*).

DISCUSSION

A new technique of contrast roentgenography of the nasopharynx is described. The

3 cases reported show the practicability of contrast study of the nasopharynx in the frontal and oblique positions, both by cinefluorography and roentgenography, with the aid of image intensification fluoroscopy. This method of examination provides not only a study of the roentgenographic anatomy, but also of the dynamics of the nasopharynx.

The findings in our cases studied so far show several unexpected features. Firstly, barium initially collects as a relatively narrow central tubular column within the nasopharynx, which we consider the central or "functional" channel (Fig. 1, *A–D;* 3*A;* 6, *A–D;* and 9*A*). It is only subsequently that the barium may fill the pharyngeal recesses, thus increasing the width of the barium column within the nasopharynx (Fig. 3*C;* 5*A;* and 9*B*). Secondly, we noted many variations in the size and shape of the nasopharynx, the discussion of which is beyond the scope of this paper. Thirdly, there was a surprisingly appreciable degree of expansion and contraction of the lateral walls of the nasopharynx during deglutition, thus indicating a great degree of pliability of these walls (Fig. 1, *A–D;* 4, *A–D;* 6, *A–D;* and 7, *A–D*).

The normal nasopharynx is said to be

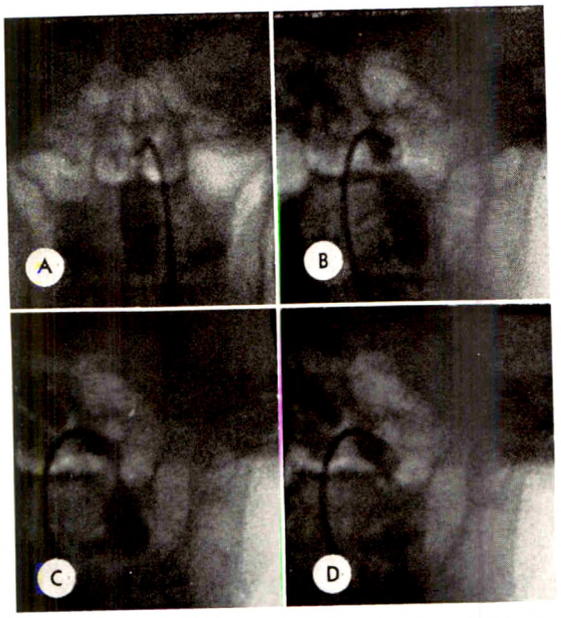


Fig. 6. Case III. *Posteroanterior cinefluorograms.* In this series, the patient's head is first in the posteroanterior position, then rotated to the right and then back to the left. (*A*) Posteroanterior view, showing thumb-shaped column of barium within the nasopharynx. (*B*) Patient's head is now rotated to the right. Early phase of swallowing with beginning contraction of upper part of nasopharynx. (*C*) There is further rotation of patient's head to the right. The upper part of the nasopharynx shows further contraction and is markedly narrowed. (*D*) Commencement of rotation of patient's head to the left. The nasopharynx is now emptied of barium except for a blob at its roof. The rest of the barium is in the lower part of the pharynx.

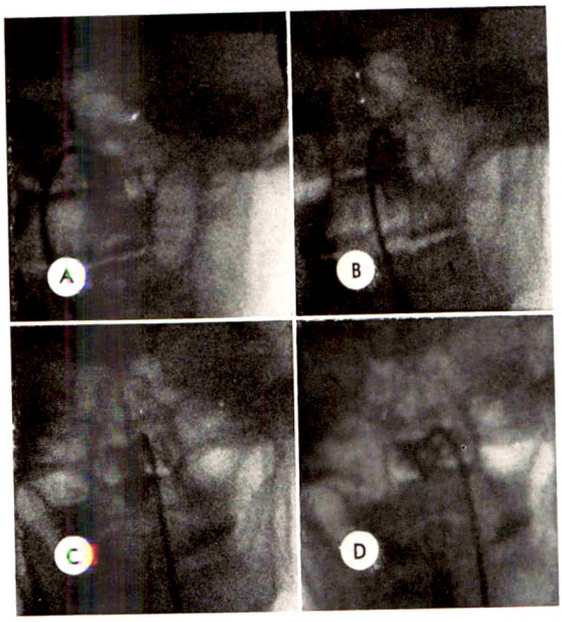


Fig. 7. Case III. *Posteroanterior cinefluorograms.* Patient's head is rotated to the right at the commencement of this series and is subsequently rotated to the left. (*A*) Patient's head is rotated to the right. It shows a good rectangular column of barium within the nasopharynx. Note that this column is slightly wider than that seen in the previous series (Fig. 6, *A–D*). (*B*) Beginning of rotation of patient's head to the left. The roof of the nasopharynx is slightly concave in this series, which probably indicates some pliability of the roof of the nasopharynx (compare with slight convexity seen in Figure 6, *A–D*). (*C*) True posteroanterior position. There is commencing contraction of the nasopharynx. (*D*) Slight rotation of patient's head to left. Moderate emptying of lower nasopharynx with some barium remaining in the roof of the nasopharynx. The rest of the barium has reached the lower pharynx.

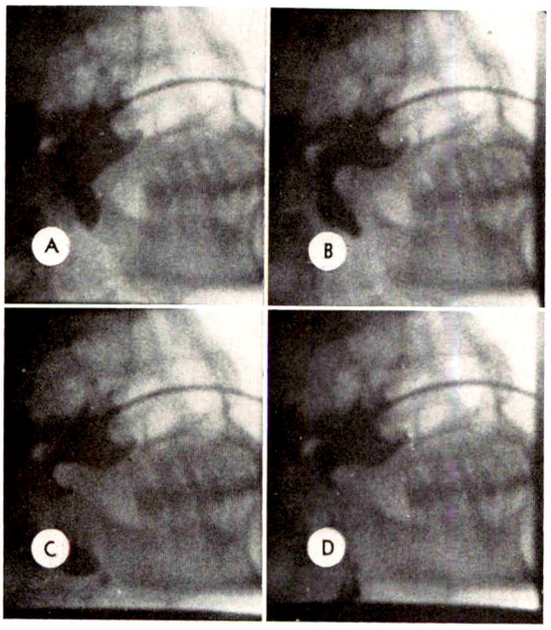


FIG. 8. Case III. *Lateral cinefluorograms.* (*A*) Good filling of the nasopharynx with wide anteroposterior diameter. Commencement of swallowing shows the early phase of contraction of the nasopharynx with slight elevation of the soft palate. (*B*) Later phase of contraction with more elevation and arching of the soft palate and moderate narrowing of the nasopharynx. (*C*) Still later phase of contraction with bolus of barium descending into lower pharynx. (*D*) Beginning of relaxation of the nasopharynx with some widening of its anteroposterior diameter and descent of the soft palate.

about 4 cm. in width,[5] but our findings indicate that the initial width of the nasopharynx, *i.e.*, the central or "functional" channel, averages about 2 cm. This unexpected finding led us to a search of the more recent literature on cinefluorography of the pharynx. We found that the frontal cinefluorograms of the oropharynx during the swallowing mechanism after poliomyelitis, made by Ardran, Kemp and Wegelius[1] showed the oropharynx as a channel of moderate width but capable of some contraction and much expansion. Roberts[10] in a study on pharyngeal deglutition shows a frontal cinefluorogram demonstrating the oropharynx as a channel of moderate width. The work of Wittenborg and Neuhauser[14] on contrast examination of the eustachian tubes is of interest. These authors present frontal roentgenograms of the eustachian tubes, but the nasopharynx is not well opacified because of the thin type of contrast substance used. Their submentovertical roentgenograms show to advantage the "functional" channel of the nasopharynx. These investigators used image intensification fluoroscopy, followed by spot roentgenography at rest, during swallowing and during a Valsalva maneuver.

The lateral roentgenogram of the contrast filled nasopharynx is familiar and has been mentioned. It is of interest to note that both Ardran and associates and also Roberts instill some contrast substance into the floor of the nasal cavities to aid visualization of the action of the soft palate and posterior wall of the pharynx in their deglutition studies with lateral cineroentgenography. We routinely perform lateral cinefluorography and spot film roentgenography to complete our study of contrast roentgenography of the nasopharynx.

Our original purpose in developing a practicable method of contrast roentgenography of the nasopharynx was to demonstrate and detect tumors of the nasopharynx. We concur with some authorities[4,11,13] that plain roentgenography, perhaps with tomography, would suffice for the detection of the majority of cases of tumors of the nasopharynx. However, our limited experience so far has shown that contrast roentgenography may sometimes help in the detection of cancer overlooked by other methods of examination. This is because any slight deviation of the barium column or a small filling defect can be easily demonstrated. Another advantage is that contrast cinefluorography provides a study of the dynamics of the nasopharynx. Thus, decreased mobility of one lateral wall of the nasopharynx as seen on cinefluorograms would be indicative of pathology of the nasopharynx, as in cases of infiltration by growth.

The handicaps of any specialized roentgenographic examination are the inconvenience to patients and the increased work

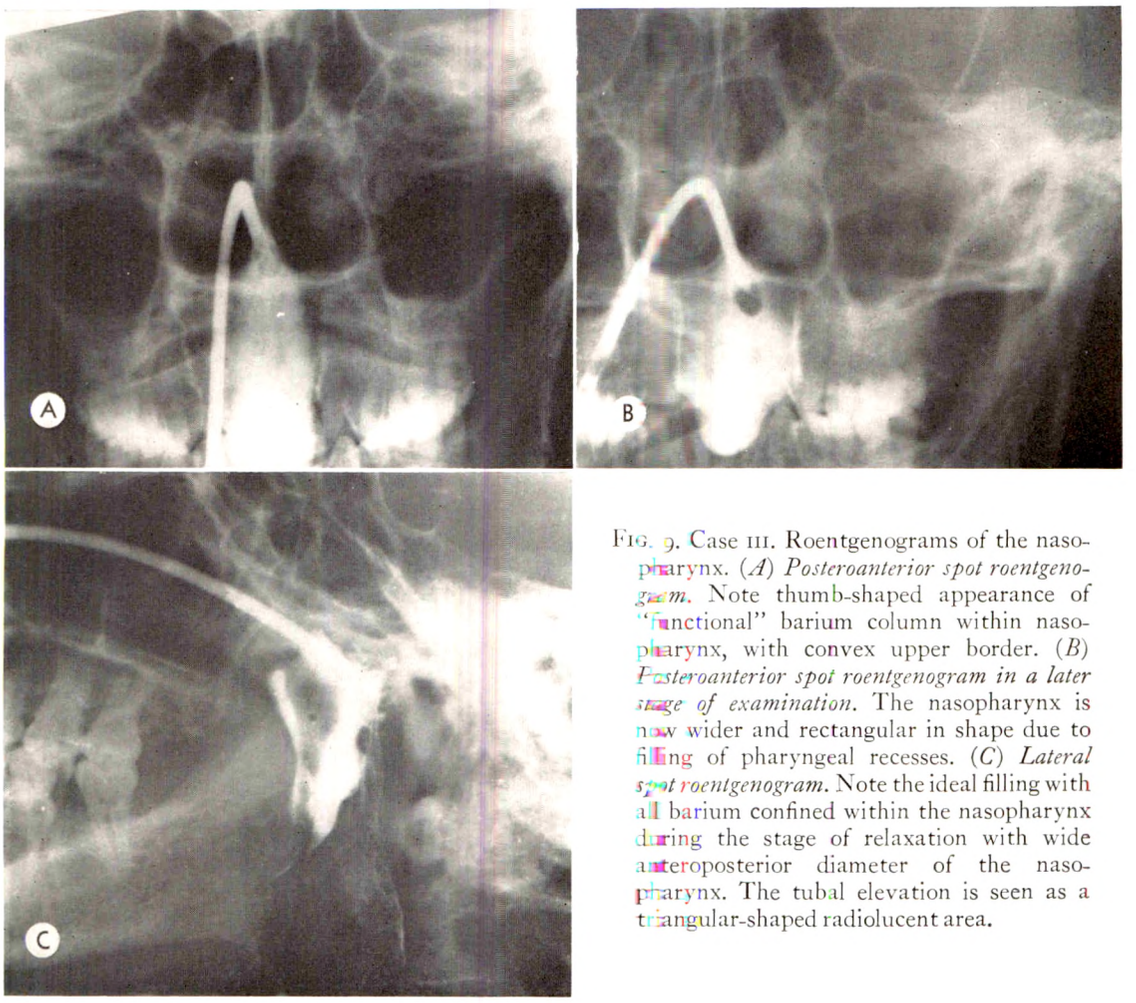


Fig. 9. Case III. Roentgenograms of the nasopharynx. (*A*) *Posteroanterior spot roentgenogram.* Note thumb-shaped appearance of "functional" barium column within nasopharynx, with convex upper border. (*B*) *Posteroanterior spot roentgenogram in a later stage of examination.* The nasopharynx is now wider and rectangular in shape due to filling of pharyngeal recesses. (*C*) *Lateral spot roentgenogram.* Note the ideal filling with all barium confined within the nasopharynx during the stage of relaxation with wide anteroposterior diameter of the nasopharynx. The tubal elevation is seen as a triangular-shaped radiolucent area.

for the staff. Contrast roentgenography of the nasopharynx is no exception to the rule, but we feel that, if judiciously employed, it has a role in problem cases.

SUMMARY

1. A new technique of contrast cinefluorography and roentgenography of the nasopharynx, with particular reference to the frontal and oblique projections, is described.

2. This method provides a satisfactory morphologic as well as dynamic roentgenographic study of the nasopharynx.

3. Unexpected normal anatomic variations and other features of the nasopharynx are demonstrated by this method of examination.

4. It is believed that contrast roentgenography can play a useful role in the detection of tumors of the nasopharynx in doubtful or obscure cases which cannot be detected by other methods of examination, including plain film roentgenography.

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This investigation is the outcome of the combined efforts of many of our colleagues. We particularly acknowledge the technical help of Messrs. Philip S. B. Law and Soon Bee Tan, who put in much time and effort in order to enable us to establish satisfactory working and exposure factors for cinefluorography, to the technical staff of Ko-

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Forty-ninth Annual Meeting: Royal York Hotel, Toronto, Ontario, Canada, May 29–31. 1967.

EDITORIALS

THE NATURE OF THE LOWER ESOPHAGEAL RING

SUFFICIENT data about the lower esophageal ring have now accumulated to permit some definite statements and some likely conjecture about its nature.

The lower esophageal ring is found at any age beyond the teens, is commoner in the older subject and is present in the majority of people over 50 years of age. It is a fixed structure that requires adequate dilatation of the esophagus for visualization. Its apparent movement, noted radiologically, may be explained by (1) movement of the entire esophagus that occurs normally during swallowing, (2) movement attendant upon variations in degree of distention of the distal esophageal segment, and (3) change in the relative position between hiatus and esophagus. The diameter of its aperture either remains the same or tends to become smaller over the years.

Chronically inflamed submucosal fibrous tissue comprises the core of the ring. With the exception of one notable case, the muscularis propria in the presence of the ring is normal; the muscularis mucosae may show local proliferation or distortion of its pattern. Most, but not all, of the rings mark the transition from squamous to columnar epithelium. Practically all the rings are said to sit atop a small sliding hiatal hernia. Rinaldo and Gahagan[1] found microscopic evidence of mild to marked inflammatory reaction in the columnar-lined mucosa a few centimeters distal to the ring in all 7 of their surgically treated patients with dysphagia.

Manometric studies of Cauthorne *et al.*[2] and of others demonstrated that the ring lies just proximal to the high pressure zone —the inferior gastroesophageal sphincter so well defined by Code and co-workers.[3] Rinaldo and Gahagan[1] found low sphincteric pressures in all their patients with rings producing dysphagia. Postlethwait and Musser[4] believe that the ring is caused by a recurrent, low-grade peptic esophagitis. Barrett[5] suggests that the ring evolves as a guard against further acid-pepsin reflux: the patient has been given the possibility of dysphagia for the price of protection against ascending esophagitis.

As regards the relationship between the ring and hiatal hernia, it may be said that, since the mucosa of the lower 2 or 3 cm. of the esophagus may normally be covered by columnar epithelium, the presence of this epithelium above the diaphragm does not necessarily indicate a sliding hiatal hernia. Since the ring lies just proximal to the high pressure zone and since normally the extension of the high pressure zone above the diaphragm should not exceed 2 or 3 cm., a ring higher than this distance above the hiatal impression must indicate proximal dislocation of the sphincter-bearing vestibule, the so-called Grade 1 vestibular hernia. Rather than hernia, this could be regarded as a degenerative loosening of the vestibular fixing apparatus due to aging. If the presence of a ring is taken to indicate a small sliding hiatal hernia, differences between this hernia and the hernia without the ring must be recognized; the hernia with the ring is always small, is not associated

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[4] POSTLETHWAIT, R. W., and MUSSER, A. W. The pathology of lower esophageal web. *Surg., Gynec. & Obstet.*, 1965, *120*, 571–575.

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with peptic stricture, is attended by dysphagia especially when the internal diameter of the ring is 12 mm. or less, is rarely associated with clinical or radiologic reflux, and is present in most people beyond the age of 50 years. The hernia without the ring, however, is small or large, may be associated with peptic stricture, is not attended by significant dysphagia in the absence of stricture, is commonly associated with clinical and radiologic reflux, and is much less common than the hernia with a ring.

That the ring is abnormal cannot be doubted. After the age of 30 years, most weight-bearing cartilages, too, are abnormal. We prefer to look upon both as degenerative phenomena, and important only when they cause symptoms. We believe that the ring is a mucosal and submucosal structure resulting from chronic inflammation, due to mild peptic esophagitis from minimal deficiency in the distal esophagogastric closing mechanism—a degenerative phenomenon of aging. We prefer to regard the presence of a ring as part of a syndrome likely to be manifested when the aperture of the ring is 12 mm. or less. This syndrome, found especially in men in their fifties who have had no weight-loss, consists of intermittent dysphagia, especially with bread and meat, and often with episodic painful impactions. We prefer to report the ring with emphasis on the diameter of its aperture, and on the relation of this diameter to the likelihood of the ring as a cause of symptoms, rather than to place the emphasis on the presence of a sliding hernia. Only if the ring is more than 3 cm. above the hiatal impression, when the esophagus is maximally dilated, is the radiologist justified in diagnosing a sliding hiatal hernia. Rings may be regarded, in short, as evidence of increased vestibular mobility, as a frequent manifestation of aging, and as an association of subclinical peptic esophagitis stemming from deficiency in the distal esophagogastric closing mechanism.

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HANS RUDOLPH SCHINZ
M.D., M.D.(HON.), D.SC.(HON.)
1892–1966

ON JUNE 12, 1966 Hans Rudolph Schinz passed away after a prolonged illness. For nearly half a century Schinz has had a tremendous influence on the development of radiology not only in Switzerland, but all over the world, and I think there would be hardly a radiologist who is not acquainted with at least some of his works.

It was in 1918 that Schinz, after his internship with Professor Eichhorst, became the predecessor of Dr. Chaoul for the radiological services of the University Hospital in Zurich. Radiology at that time was a

rather unimportant branch of medicine. Two modest rooms were at his disposal: one for diagnostic tests and one for research and radiation treatments. Today, the University of Zurich has one of the best equipped radiological institutes with excellent facilities for diagnosis and therapy.

The development from a two-room limitation to a most superb radiological institute is to a great extent the result of Schinz's dynamic personality and his vigor to improve and to progress. It was a fortunate coincidence that Schinz entered his medical career at the time when radiology was still in its initial developmental stages. He came from an aristocratic family, which during a period of over 400 years resided in Zurich and produced many scholars. Schinz had, therefore, inherited unusual abilities for research. He possessed a brilliant way of foreseeing problems and attacking them in a straightforward manner.

Radiology, relatively undeveloped at that time, was just waiting for Schinz in order to still his hunger for research activities. He was masterful in the selection of his co-workers for the particular tasks he wanted investigated. Schinz was first mainly interested in diagnostic problems, but soon began experimental work in radiation biology and became intensely interested in radiation therapy. He introduced many new and revolutionary treatment methods. He was equally eager to set up programs for the instruction of the population for early detection of cancer, prophylactic measures and the advance in cancer research.

When Schinz entered Radiology no satisfactory textbook was available. In conjunction with Baensch and Friedl, he created a work which appeared for the first time in 1928. It was appreciated not only by radiologists, but also by the rest of the medical profession. This textbook has just been published in its sixth edition and Schinz's influence and contribution to this newest edition was no less than in any previous edition. The writer of these lines, when visiting Schinz in October of 1965, was amazed at how minutely he checked the galley proofs and applied his corrections.

Schinz's contributions to teaching are eminent. Today it is very difficult to imagine the situation 40 to 50 years ago when radiology was regarded as relatively unimportant. It was only in 1935 that radiology was declared as a compulsory subject in medical teaching in Zurich, mostly on the grounds of Schinz's efforts. Schinz caused the founding of the Organization of the Academic Teachers of all countries, and he was very pleased when in 1965 in Rome he was chosen as the Honorary President. In 1934 he was President of the Fourth International Congress of Radiology, which he organized splendidly and which was held in Zurich and St. Moritz, Switzerland. Schinz was an Honorary Member of the American Roentgen Ray Society and more than 20 other societies. The Stuttgart Institute of Technology gave him an Honorary Doctor of Science Degree in 1958 and on his 70th birthday he obtained an Honorary Medical Doctors Degree from the University of Tübingen. There are innumerable other honors Schinz received during his lifetime.

His contributions to the science of radiology are reflected in his large number of publications and books. Besides all the honors he received throughout his fruitful life and all his contributions to the science of radiology, there is one major contribution which has to be mentioned and that is his influence on hundreds and hundreds of people who worked with him during nearly half a century. Schinz was a hard worker with an efficiency which could hardly be matched. By the same token he was equally demanding of his staff. His way of thinking was passed on to many of his students and co-workers and I think we can say that Schinz will continue to live in the achievements of his students. Those who knew Schinz personally feel particularly saddened by the loss of this great man. Any conversation with Schinz was always a special ex-

perience. He was modest about his achievements and so eager to learn something new. His wide field of interest was astonishing and went far beyond the clinical aspects of radiology, covering physics and many other fields in the natural sciences. His knowledge then, especially in physics, was far beyond that which would be expected of a radiologist.

His brilliance, the ease with which he expressed himself, and his sense of humor made him an excellent teacher and an unforgettable person.

WALTER MAUDERLI, D.Sc.

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NEWS ITEMS

THE ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

At the last Annual Meeting of the Rocky Mountain Radiological Society, the following new officers were elected for 1967:

President: John H. Freed, M.D., Englewood, Colorado; *President-Elect:* Bertram L. Pear, M.D., Englewood, Colorado; *First Vice-President:* George D. Davis, M.D., Rochester, Minnesota; *Second Vice-President:* C. N. Sorensen, M.D., Scottsbluff, Nebraska; *Secretary-Treasurer:* Robert W. Lackey, M.D., 4200 East Ninth Avenue, Denver, Colorado 80220; and *Historian:* H. Milton Berg, M.D., Bismarck, North Dakota.

The next Annual Meeting of the Society will be held in Denver at the Brown Palace Hotel on August 17, 18 and 19, 1967.

THE CANADIAN ASSOCIATION OF RADIOLOGISTS

The Thirtieth Annual Meeting of the Canadian Association of Radiologists will be held at the Skyline Hotel, Toronto, Ontario, February 28–March 5, 1967. The scientific portion of the program will be held Wednesday to Sunday, March 1–5.

All communications should be addressed to the Chairman of the Central Scientific Program Committee, The Canadian Association of Radiologists, Suite 511, 1555 Summerhill Ave., Montreal 25, Ontario, Canada.

SYMPOSIUM ON RADIOTHERAPY AND DIAGNOSIS OF TUMORS OF THE CENTRAL NERVOUS SYSTEM

The University of Miami School of Medicine, Department of Radiology, will present a "Symposium on Radiotherapy and Diagnosis of Tumors of the Central Nervous System," January 13–15, 1967, at the Eden Roc Hotel, Miami Beach, Florida.

In addition to the local Faculty the following distinguished Guest Speakers will participate in the program: H. M. Zimmerman, M.D., New York, New York; Florence Chu, M.D., New York, New York; Jean Bouchard, M.D., Montreal, Canada; Ivor Fix, M.D., Miami Beach, Florida; Simon Kramer, M.D., Philadelphia, Pennsylvania; Guy L. Odom, M.D., Durham, North Carolina; Juan A. del Regato, M.D., Colorado Springs, Colorado; and Gordon D. Potts, M.D., New York, New York.

For further information contact Dr. Mario Vuksanovic, Radiation Therapy Division, University of Miami, Jackson Memorial Hospital, P. O. Box 875, Biscayne Annex, Miami, Florida 33152.

COURSE IN MEDICAL USES OF RADIOACTIVE ISOTOPES

A four month 90 hour course in the Medical Uses of Radioactive Isotopes will be offered at the Queens Hospital Center by the Nuclear Medicine Division.

The course will be held February 7 through June 6, 1967, on Tuesdays, 1:00 P.M. to 6:00 P.M., and will consist of weekly five-hour sessions covering lectures, laboratory exercises and clinical management of patients.

The enrollment is limited to 15.

For further information write to Division of Nuclear Medicine, The Long Island Jewish Hospital, Queens Hospital Center Affiliation, 82–68 164th Street, Jamaica, New York 11432.

COURSE IN NEURORADIOLOGY COLUMBIA-PRESBYTERIAN MEDICAL CENTER

The Department of Radiology, College of Physicians and Surgeons, Columbia University, announces a postgraduate course in Neuroradiology to be held at the Columbia-Presbyterian Medical Center, April 10–14, 1967.

The course is designed primarily for radiologists but physicians in other specialties are welcome to attend. Emphasis will be placed on basic information used frequently by the radiologist, especially

angiography. Topics of the course will also include plain skull film diagnosis, pneumography, myelography, systemic disease affecting the central nervous system and neuroradiologic approaches to the solution of specific clinical problems.

Inquiries should be addressed to the Program Director, Ernest H. Wood, M.D., Neurological Institute of New York, 710 West 168th Street, New York, New York 10032.

WORKSHOP IN PEDIATRIC RADIOLOGY

The first Annual Workshop in Pediatric Radiology will be held at the Children's Mercy Hospital, Kansas City, Missouri, April 24–28, 1967.

Guest Professor will be John Caffey, M.D.

Only 10 registrants will be accepted which permits the curriculum to include participation in daily patient care, special procedures, Guest Professor lectures, teaching file seminars, and scientific exhibits review.

For further information write to Charles E. Shopfner, M.D., Professor of Radiology, University of Missouri School of Medicine; and Head, Department of Radiology, Children's Mercy Hospital, 1710 Independence Avenue, Kansas City, Missouri 64106.

COURSE IN DIAGNOSTIC RADIOLOGY OF THE SKELETAL SYSTEM

A five day course in Diagnostic Radiology of the Skeletal System will be presented at the Albert Einstein College of Medicine under the sponsorship of the Albert Einstein College of Medicine and its affiliated hospitals, including the College Hospital, Jacobi Hospital, and the Montefiore Hospital and Medical Center. The course will be given from May 15th to May 19th, 1967.

In addition to the members of the faculty of the Medical College, the course will include the following guest speakers: David H. Baker, M.D., Robert H. Freiberger, M.D., Henry L. Jaffe, M.D., John E. Moseley, M.D., Alex Norman, M.D., all of New York City; John Caffey, M.D., of Pittsburgh, Pa.; David C. Dahlin, M.D. of Minneapolis, Minn.; Jack Edeiken, M.D. of Philadelphia, Pa.; Melvin Glimcher, M.D. of Boston, Mass.; Lent C. Johnson, M.D. of Washington, D. C.; Gwilym S. Lodwick, M.D. of Columbia, Mo.; Ronald O. Murray, M.D. of London, England; Edward B. D. Neuhauser, M.D. of Boston, Mass.; and Howard L. Steinbach, M.D. of San Francisco, Calif.

For further information please write to Harold G. Jacobson, M.D., Program Director, Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, New York 10467.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the Clinical Use of Radioactive Isotopes will be given under the supervision of Dr. Sergei Feitelberg, Dr. Solomon Silver and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 5 through June 30, 1967. This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens. In addition to Drs. Feitelberg, Silver and Quimby, the teaching staff will include a number of invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, New York 10029.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Radiology of the Digestive System: A Radiological Companion to Truelove and Reynell's Diseases of the Digestive System. By K. Lumsden, M.A., N.B., B.Chir., D.M.R.E., Consultant Radiologist, Radcliffe Infirmary, Oxford; Clinical Lecturer in Radiology, University of Oxford; and S. C. Truelove, M.A., M.D., F.R.C.P., Nuffield Department of Clinical Medicine, University of Oxford. Cloth. Pp. 548, with 530 illustrations. Price, $22.50. F. A. Davis Co., 1914–16 Cherry Street, Philadelphia, Pa., 1965.

In organizing a compact, survey type handbook outlining the radiological dimensions of the digestive system, the authors, a radiologist and an internist, have collaborated beautifully to produce a radiological companion to the gastroenterologically oriented "Diseases of the Digestive System." Continuity between the two books is provided by Dr. Truelove who co-authored both books, collaborating with Dr. P. C. Reynell on the first.

Following the opening chapter on the basic principles of radiology, and the production of the radiographic and fluoroscopic image, the subsequent chapters systematically explore the advantages and limitations of the radiological examination of the entire alimentary tract, including the diaphragm, peritoneal cavity, and accessory organs of the liver, pancreas, and biliary tract. There are also sections devoted to the examination of the newborn child and the acute abdomen. The subject material is quite comprehensively covered in an easily readable form and is illustrated with superior quality roentgenographic reproductions and several line drawings and tables. Both normal and abnormal appearances are described and pertinent etiological and clinical information is given. Of necessity, exhaustive detail and minutia are not included, but this serves only to increase the usefulness of this book to the group for which it was prepared, namely the average physician and surgeon. It was felt that, because of the important role which radiology plays in the diagnosis of diseases of the digestive system, every doctor should have some understanding of the scope of the various radiological investigations applicable to this system.

This book obviously was not intended for the expert radiologist or highly trained gastroenterologist, but it can be recommended for study to medical students, generalists, physicians and surgeons of other specialties, beginning radiology residents, and allied paramedical personnel. The interested reader will be rewarded with basic encompassing information of the radiologically definable abnormalities of the gastrointestinal system.

Donald M. Monson, M.D.

Pathology of Bone. By the late Douglas H. Collins, O.B.E., M.D., F.R.C.P., F.C. Path., Formerly Professor of Pathology, University of Sheffield, Honorary Consultant Pathologist, United Sheffield Hospitals (Royal Infirmary and Sheffield Regional Hospital Board (Sheffield National Centre for Radiotherapy). Prepared for publication by O. G. Dodge, M.D., M.C. Path., Consultant Pathologist, Christie Hospital and Holt Radium Institute, Manchester; Formerly Senior Lecturer in Pathology, University of Sheffield. Cloth. Pp. 254, with many illustrations. Price, $14.50. Butterworth Inc., 7300 Pearl Street, Washington 14, D. C., 1966.

At the time of his death in 1964, Professor Collins had completed 10 chapters on the pathology of non-neoplastic diseases of bone. The scope and purpose of the book as Professor Collins conceived it, is conveyed in the following abstract from an unpublished manuscript.

"It is no longer possible to describe the pathological anatomy and histology of bone in any meaningful way without constant reference to the dynamic functions of cells, and the movements of mineral and organic materials. Nor is it proper to write of bones as though they comprised a wholly independent system. The pathology of bone must be seen in the context of the functioning body as a whole, in particular, of the kidneys, the endocrine glands, and the alimentary and haemopoietic systems. In writ-

ing this book, I have had two objectives constantly before me, namely to provide the advanced student, and in particular the postgraduate who is in training in Pathology, Orthopedics or Radiology with a textbook outlining the pathological basis of bone disease, and secondly to provide a reasonably comprehensive work of reference to which the practicing pathologist, radiologist or surgeon could turn when faced with a diagnostic difficulty."

At the time of his death in 1964, Collins had written only the first 10 chapters, and part of the 11th chapter. The bulk of the uncompleted chapters would have dealt with the dysplasias and neoplasms of bone.

The opening chapter of the book is characteristically lucid, and includes an outline of the structure, chemistry, development and growth of osseous tissue. The theme of all the succeeding chapters is that the pathological states of this tissue, whether due to mechanical or chemical injury, vitamin deficiency or excess, endocrine or metabolic disorders, and infections, are to be understood as deviations from the normal structural and functional state—briefly that pathology is extended physiology.

Most of the pathological material on which the book was based was sent to Dr. Collins by pathologists and surgeons from many parts of the world.

Chapters are devoted to fracture repair and bone grafts; pathological formations of new bone; rickets, osteomalacia, scurvy and other effects of vitamins; and osteoporosis and other atrophic conditions. In addition, further chapters are devoted to the bone lesions of endocrine disease including an extensive chapter on parathyroid disease. Bone changes in various diseases of the kidney are also discussed in detail.

Focal histiocytic lesions of bone, lipidoses and other metabolic diseases, as well as changes induced in bone by radiation and chemical toxins make up additional chapters.

The present publication consists of 12 chapters; the last 2 chapters are written by O. G. Dodge, M.D., M.C., and are devoted to infective disease and Paget's disease of bone.

The subspecialist within the specialty may wish for some greater detail on various subjects, but for general diagnostic purposes, the authors have succeeded splendidly in their objectives. The illustrations are excellent, and the concise style of writing makes for easy reading and understanding.

This book on pathology of bone should prove to be of considerable interest not only to pathologists, but to all radiologists as well.

E. Nicholas Sargent, M.D.

BOOKS RECEIVED

The Diagnosis of Hydatidiform Mole, Malignant Hydatidiform Mole and Choriocarcinoma with Special Reference to the Diagnostic Value of Pelvic Arteriography. By Ulf Borell, M.D., Professor of Obstetrics and Gynaecology, Karolinska Institutet; Head, Department of Women's Diseases, Karolinska Sjukhuset, Stockholm, Sweden; Ingmar Fernström, M.D., Associate Professor, Karolinska Institutet; Department of Diagnostic Roentgenology, Karolinska Sjukhuset, Stockholm, Sweden; Gunnar Moberger, M.D., Associate Professor, Institute of Radiopathology, Karolinska Sjukhuset, Stockholm, Sweden; and Lars Ohlson, M.D., Department of Diagnostic Roentgenology, Karolinska Sjukhuset, Stockholm, Sweden. Cloth. Pp. 110, with many illustrations. Price, $9.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1966.

Atomic Energy and Southern Science. By William G. Pollard. Paper. Pp. 148. Oak Ridge Associated Universities, Inc., Oak Ridge, Tenn., 1966.

Computer Calculation of Dose Distributions in Radiotherapy. Report of a Panel held in Vienna, October 18–22, 1965. Technical Reports Series No. 57. Paper. Pp. 215. Price, $4.50. International Atomic Energy Agency, Vienna, 1966. In U.S.A., International Publications, Inc., 319 East 34th Street, New York, N. Y., 1966.

Radiation Therapy of Tumors and Diseases of the Nervous System. By Jean Bouchard, M.D., F.A.C.R., F.R.C.P.(C), Professor of Radiology, McGill University; Consultant in Radiation Therapy, Montreal Neurological Hospital; Chief, Department of Therapeutic Radiology, Royal Victoria Hospital, Montreal, Quebec, Canada. Cloth. Pp. 244, with some illustrations. Price, $10.50. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa., 1966.

Biophysical Aspects of Radiation Quality. Report of a Panel on Biophysical Aspects of Radiation Quality held in Vienna, March 29–April 2, 1965. Technical Reports Series No. 58. Paper. Pp. 186, with some figures. Price, $4.00. International Atomic Energy Agency, Vienna, 1966. In U.S.A., International Publications, Inc., 319 East 34th Street, New York, N. Y., 1966.

Planning Guide for Radiologic Installations. Second edition. Edited by Wendell G. Scott, M.D. By the Committee on Planning of Radiologic Installations of the Commission on Public Relations of the American College of Radiology. Cloth. Pp. 297, with some illustrations. Price, $9.50. Williams & Wilkins Company, Baltimore 2, Md., 1966.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

Vulliamy, David G., and Normandale, Peter A. Cranio-facial dysostosis in a Dorset family. *Arch. Dis. Childhood*, Aug., 1966, *41*, 375–382. (From: West Dorset Medical Society for Postgraduate Education and Research, Dorset County Hospital, Dorchester, England.)

Crouzon's disease or hereditary cranio-facial dysostosis was first described in 1912. Outstanding findings are varying degrees of deformity of the skull, bilateral exophthalmos, a beaked nose, a hypoplastic maxilla, and a narrow arched palate. The skull malformation has been shown to be due to premature fusion of cranial sutures. In Apert's disease (acrocephalosyndactyly) the premature craniosynostosis is associated with variable degrees of syndactyly. It is this associated malformation rather than the precise extent of the craniosynostosis which is the guiding factor in differential diagnosis between Apert's disease and Crouzon's disease, the facial features of the latter being distinctive.

The authors describe a family in which 14 members were affected, and by presenting the family tree confirm the transmission by a hereditary mendelian dominant mode. Numerous photographs and roentgenographic reproductions are included to demonstrate the pertinent features.—*Donald S. Linton, Jr., M.D.*

Lapayowker, Marc S., Murtagh, Frederick, and Kirkpatrick, John A. Echoencephalography in the evaluation of hydrocephalus. *Radiology*, June, 1966, *86*, 1052–1055. (From: Departments of Radiology and Neurosurgery, Temple University Hospital, and St. Christopher's Hospital for Children, Philadelphia, Pa.)

Echoencephalography has shown considerable value in demonstrating the midline structures of the brain. The authors discuss the use of ultrasound in evaluating the position of the lateral wall of the lateral ventricle in hydrocephalus, with lateral ventricle dilatation. While the normal position of the ventricular wall "echo" varies somewhat due to variations in its curvature, placement of the transducer 2–4 cm. above the ear and differences in power output and detector sensitivity will result in a satisfactory demonstration in most cases. It is important that transducer position be carefully marked so that comparable future follow-up examinations can be obtained, and that only the "far-side echo" be evaluated, since the "near-side echo" is often distorted by the skull. Potentially confusing island of Reil echoes can usually be identified by vascular pulsation.

Fifteen patients were examined with pneumoencephalography or ventriculography, and the position of the lateral wall echo correlated well with the lateral wall position on air studies.

The authors feel that this easily performed and atraumatic procedure is a valuable and reliable method for the demonstration and follow-up of hydrocephalus, when used by an experienced examiner.—*J. A. Cunyus, M.D.*

Abdomen

Wichtl, O. Zur Röntgenuntersuchung des Dickdarms auf oralem Wege. (Oral roentgen examination of the colon.) *Wien. klin. Wchnschr.*, May, 1966, *78*, 382–389. (From: Krankenabteilungen für chronische und Altersleiden des Altersheimes Baumgarten in Wien, Austria.)

Roentgen examination of the colon following the administration of a barium enema occasionally meets with great difficulty. Elderly patients as well as infants tend to be unable to cooperate properly. The following causes of poor results are cited: (1) insufficient sphincter control; (2) rectal and hemorrhoidal operations; (3) anal fissures and bleeding hemorrhoids; (4) serious illness, paralysis, and mental deterioration; (5) rejection of an enema; and (6) inability to retain the enema fluid. Enema studies also are contraindicated when perforations are suspected, as in carcinoma, diverticula, and stercoraceous ulcers.

In view of encountered technical difficulties with barium enemas in geriatric practice, the author resorted with increasing frequency to oral administration of the contrast material. Gastrografin was found to be ideal for this purpose as its absorption from the intestinal tract amounted to only 2 per cent. The medium also had a marked laxative effect and promoted the evacuation of disturbing stercoral material from the colon. Thirty ml. of gastrografin was mixed with 100 gm. of barium sulfate and sufficient water to make a solution of 200 ml. Roentgen study was started 9 to 12 hours after ingestion of a first dose and 3 to 5 hours after a second dose of the mixture.

Indications for the oral method are: (1) suspected partial or complete intestinal stenosis; (2) acute hemorrhages; (3) impending perforation of a peptic ulcer or diverticulum; (4) other acute surgical conditions; (5) testing of surgical resections; (6) foreign bodies and tumors prior to endoscopy; (7) gastrointestinal fistulae; and (8) megacolon.

The disadvantage of the method is small-intestinal irritation with decreased opacity and an inadequate mucosal relief, which was manifest only when the barium mixture and water were omitted. The advantages are a marked density of the contrast mixture and its laxative effect.

No harmful results were experienced even when in-

complete intestinal obstruction was present. The method was tested in 101 mostly geriatric patients with an average age of 78.2 years in 92 of these. Carcinoma of the colon was found in 7 patients, extraintestinal carcinoma in 4, gastric cancer in 1, and diverticulosis in many of the elderly.—*Ernest Kraft, M.D.*

Mosca, Lidio G., Sanchez, L. Arrieta, and Astrada, Horacio. Valor de la prueba de Chudacek en la colangiografía intravenosa negativa y su modificación medicamentosa. (Value of Chudacek's test in negative intravenous cholangiography and its medical modification.) *Radiología*, March, 1966, *16*, 46–50. (From: Servicio de Cirugia General, Hospital Córdoba, Córdoba, Rep. Argentina, and Servicio de Radiología, Hospital Santo Tomás, Panamá, Republica de Panamá.)

Twenty-four hours after intravenous cholangiography fails to opacify the liver there may be opacities in the colon shown on an abdominal roentgenogram. This indicates that the contrast medium has been eliminated by the liver slowly. If no opacities are present in the colon after 24 hours, this usually indicates that there is hepatic insufficiency.

In a great number of cases in which the gallbladder was not opacified following intravenous cholangiography, and in which opacities were shown in the colon 24 hours later, antibiotics or corticoids were given for 4 days. On the 5th day many of these patients showed a positive intravenous cholangiographic opacification of the gallbladder or bile ducts. Therefore, it is recommended that if the biliary system is not visualized on intravenous cholangiography, and especially if the colon opacities are shown, the patient should have antibiotics or corticoids and the examination repeated in 5 days.—*Charles M. Nice, Jr., M.D., Ph.D.*

Castell, Donald O., and Johnson, Raymond B. The ^{198}Au liver scan: an index of portal-systemic collateral circulation in chronic liver disease. *New England J. Med.*, July 28, 1966, *275*, 188–192. (From: Department of Internal Medicine, United States Naval Hospital, Great Lakes, and United States Naval Hospital, Bethesda, Md.)

The authors report the use of the colloidal gold liver scan as a means for evaluation of the extent of chronic liver disease in 20 patients. The scans were interpreted according to specific objective criteria of degree of liver "mottling," splenic uptake of radioactive tracer and bone marrow uptake. The total "liver scan score" for each patient was found to agree favorably with the results of an oral ammonia tolerance test.

Their results indicate that the degree of liver involvement may be predicted from the colloidal gold scan particularly as it relates to the degree of portal system collateral circulation or portal hypertension of such patients. Thus, the authors suggest that the colloidal gold hepatic scan offers the clinician a safe, easy procedure for evaluation of the extent of chronic liver disease.—*Merle K. Loken, Ph.D., M.D.*

Genitourinary System

Glanville, J. N., and Herlinger, H. Normal hydration urography. *Clin. Radiol.*, July, 1966, *17*, 230–236. (From: Radiodiagnostic Departments of St. James's and Chapel Allerton Hospitals, Leeds, England.)

A method of intravenous urography involving the rapid injection of 50 ml. conray 280 (methylglucamine iothalamate 60 per cent) in patients who are normally hydrated is described. The intravenous pyelogram should achieve a complete and accurate demonstration of the urinary tract.

Drip infusion pyelography was described by Schencker in 1964. Glanville and Herlinger consider it impractical for the following reasons: Lavish and expensive dosage precludes its routine use; the intravenous addition to the contrast medium of about 150 ml. of water is unnecessary in a normally hydrated patient; the empirically determined contrast dose is higher than required for the purpose of the examination and the technique demands drip infusion, which adds the cost of a disposable infusion set and the time of assembling and using it.

In normal hydration urography the authors consider bowel preparation unnecessary. Diet and fluid intake are not restricted. If recent fluid intake is in doubt, a 10 ounce cup of water is given prior to the examination. Preliminary roentgenograms of the abdomen and of the bladder are taken. A ureteric compression device (Steinert, 1952) adapted to have Velcro fasteners is placed in position and left uninflated. Fifty ml. of conray 280 is injected in approximately 45 seconds. (Intravenous dosages used in children are: Under 1 year, 10 ml.; at 3 years, 15 ml.; at 9 years, 30 ml.; and at 15 years and over, 50 ml.) A roentgenogram of the kidneys and upper ureters is taken at 3 minutes. The compression device is inflated at 5 minutes and additional roentgenograms of the renal areas are taken at 10 minutes and 15 minutes. A compression release roentgenogram of the entire abdomen and pelvis is obtained immediately following the rapid release of compression. A roentgenogram of the bladder is then taken, and, if indicated, a post-micturition roentgenogram.

Comparison of the standard technique in 200 patients with the normal hydration urography technique in a like number of patients was made. The results with normal hydration urography were found to be definitely better than with the standard technique in delineation of the kidneys, calyces, pelves,

ureters and bladder. Additional examinations (retrograde pyelography) are reduced, preliminary preparation of the patient is unnecessary, and 8 degree angle tomography (zonography), done before release of the ureteric compression, yields an optimum of diagnostic information in chronic renal failure where pyelographic density is poor in the presence of good calyceal filling.

The side effects of the rapid injection of 50 ml. dose of conray 280 were negligible and no serious complication occurred.—*Samuel G. Henderson, M.D.*

HARTLEY, W. Infusion urography. *Clin. Radiol.*, July, 1966, *17*, 237–241. (From: Royal Infirmary, Edinburgh, Scotland.)

The author reports the results of 3 different techniques in excretory urography.

1. *Standard technique.* In this technique, the usual preliminary preparation by laxatives or enemas, light diet, and overnight fluid intake restriction is followed by intravenous injection of 20 ml. of sodium diatrizoate 45 per cent, or sodium acetrizoate 60 per cent, using the first 0.5 ml. as a sensitivity test. Lower abdominal compression is applied and films are exposed at 7, 12 and 20 minutes.

2. *Double dose technique.* This is similar to the standard technique, but 40 ml. contrast medium instead of 20 ml. is injected.

3. *Infusion technique.* Renal impairment was the most common indication for this technique which is patterned after that described by Schencker in 1964. The author employs 80 ml. contrast medium in 200 ml. 5 per cent dextrose solution. No special preparation of the patient was made. The contrast medium in glucose solution was infused rapidly (6 to 10 minutes) through a large needle. Films were exposed at 10, 20 and 30 minutes after beginning the injection. No compression was applied. Comparison of the results in 200 cases using Technique 1, in 100 cases with Technique 2 and in 100 cases using Technique 3 was made. In addition, 76 of the 100 cases in which Technique 3 was employed had previously been examined using Technique 1.

The infusion technique was found best of the 3 in demonstration of renal outlines, the calyceal systems and the ureters.

The author recommends this technique either as a primary method of investigation in cases of renal failure or as a second technique if the standard method is unsuccessful. However, if the fasting blood urea level is above 120 mg. per cent, diagnostic results are not obtained by the infusion technique.—*Samuel G. Henderson, M.D.*

COBB, OLIVER E. Carbuncle of the kidney. *Brit. J. Urol.*, June, 1966, *38*, 262–267. (From: Urological Unit, St. Thomas' Hospital, London, England.)

Carbuncle of the kidney is an uncommon form of renal infection and an unusual cause of renal enlargement. Up to 1965, approximately 210 cases had been reported and the author adds 4 new cases. The term "carbuncle of the kidney" is not a distinct pathologic entity so much as representing a stage in the development of untreated cortical abscesses. The etiology of the renal carbuncle is most commonly a hematogenous infection following a suppurative skin lesion such as a furuncle, carbuncle or felon. Other less common sites of infectious spread which have been reported are acute osteomyelitis, dental extraction, breast abscess, infected laceration, insect bite and respiratory infection.

The primary focus is in the renal cortex; and the usual pathogen is *Staphylococcus aureus*. The presence, however, of a renal staphylococcal infection by no means implies eventual carbuncle development. There is usually a latent period of weeks or months between the onset of symptoms and the establishment of the diagnosis. The condition is most common in young adults. Renal trauma seems to have no role in the development of the lesion but partial ureteral obstruction may be a predisposing cause. A palpable mass is often present, and the kidney is fixed during inspiration and expiration.

The usual laboratory findings are leukocytosis, elevated sedimentation rate, sterile urine culture, but no significant albuminuria as would be expected in pyelonephritis. The roentgenographic findings are an indistinct psoas muscle and irregular or obscured kidney outline and there may be calyceal and infundibular compression and distortion from the enlarged intrarenal inflammatory mass. When there is associated lateral spinal curvature away from the affected side, perinephric abscess must be strongly considered. In one of the reported cases, although laboratory, physical and intravenous pyelographic findings were present, the possibility of a cyst or tumor could not be excluded. Selective renal arteriography revealed irregular lower pole cortical filling defects which did not show a pathologic circulation compatible with neoplasm. Antibiotic therapy produced a complete remission of symptoms and repeat arteriography 1 month later showed almost complete resolution of the filling defects.

The author feels that with the aid of renal arteriography, renal carbuncle should prove to be a diagnosis more easily and definitively made and a condition cured more often with appropriate early antibiotic therapy.—*James R. Knapp, M.D.*

MCELROY, J. R. Traumatic rupture of the renal pelvis with haematoma formation and hypertension. *Brit. J. Urol.*, April, 1966, *38*, 145–148. (From: Mayday Hospital, Thornton Heath, Surrey, England.)

A detailed and well documented case of hypertension secondary to traumatic rupture of the renal pelvis with hematoma is reported.

Sixteen years prior to admission the patient received a football injury to the right kidney area. This injury resulted in the formation of a mass in the right kidney area, hematuria, and a nonfunctioning right kidney. At the time of injury, conservative therapy was followed.

The patient entered the hospital with symptoms and findings of cerebral thrombosis complicating hypertension.

Subsequent study revealed a large, partially calcified double cystic-appearing mass in the right kidney region. Intravenous pyelography demonstrated a nonfunctioning right kidney. Retrograde pyelography showed a dilated right renal pelvis perched on top of the calcified mass.

Surgical removal of the right abdominal mass and kidney was accomplished with return of the blood pressure to normal.

Pathologic study revealed an old traumatic rupture of the renal pelvis with cyst formation, fibrosis and calcification.

The author advises careful follow-up for an indefinite period in cases of renal injury by serial radiographic studies of the renal system.—*George A. Miller, M.D.*

Rosenthall, Leonard. Radionuclide diagnosis of renal cysts and neoplasms using the gamma-ray scintillation camera: preliminary work. *J. Canad. A. Radiologists*, June, 1966, *17*, 85–86. (From: Department of Radiology, Montreal General Hospital, Montreal, Quebec, Canada.)

This is a preliminary report on the use of the scintillation camera for study of renal cysts and neoplasms following the rapid administration of technetium 99m into an antecubital vein. The bolus can be traced through the major vessels by serial scintiphotograms. A time lapse study of this sort permits data to be accumulated on filling defects in renal tissue. A "blush" with renal tumors permits their differentiation from a cyst of the kidney.

The serial scintiphotos are compared to conventional scans or scintiphotograms of the kidneys obtained using a radioisotope which remains essentially "fixed" in renal tissues.—*Merle K. Loken, Ph.D., M.D.*

Anderson, E. Everett, and Wilson, Richard E. Radioisotope renography and radioscintillation scanning in the diagnosis of homograft rejection. *Surg., Gynec. & Obst.*, June, 1966, *122*, 1273–1277. (From: Department of Surgery, Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass.)

The success of renal homotransplantation depends on early recognition and treatment of homograft rejection. The clinical manifestations of this may be both local and systemic and may be confused with acute tubular necrosis, infection and obstruction of the vascular or urinary tract.

Radioisotope renography has proven valuable as a means of detecting early rejection of the homograft. Renograms are obtained on the first postoperative day, every 3rd day during the first 3 postoperative weeks and then every 5 days until the patient is discharged from the hospital. Additional daily renograms are taken whenever there is clinical or laboratory evidence of rejection. Radioisotopic renal scanning is performed after the radioactive renogram. This is done as an initial baseline procedure when the patient's clinical status is stabilized. It is then performed when rejection is threatened. The scintillation probe is easily positioned over the graft as the kidney is palpable with the patient in the supine position.

The rejection phenomenon is evident on the renograms by a decrease in the initial phase and a flattening of the secretory slope. The renal scan reveals enlargement of the homograft with diminished uptake of the radioactive material. The scan is not as sensitive as the renogram in detecting incipient rejection. Following successful treatment of the threatened rejection these studies return to their normal baseline appearance.—*David Morse, M.D.*

Wolf, James S., O'Folghludha, Fearghus T., Kauffman, H. Myron, and Hume, David M. Prolongation of renal homograft survival by indwelling beta irradiation. *Surg., Gynec. & Obst.*, June, 1966, *122*, 1262–1268. (From: Departments of Surgery and Radiation Physics and the Strauss Surgical Research Laboratories, Medical College of Virginia, Richmond, Va.)

The role of the lymphocyte in the production of transplant immunity is becoming more clearly delineated. Antibody production and possibly the ultimate destruction of the homograft is related to lymphocyte activity.

Lymphopenia produced by thoracic duct fistula and by heterologous antilymphocyte serums prolong skin homograft survival. Extracorporeal irradiation of the circulating blood produces lymphopenia.

A method of producing lymphopenia by the intra-arterial (abdominal aorta) placement of a Y^{90} beta emitting implant is described. This resulted in a lymphopenia without systemic reaction. Significant survival of the renal homograft of the Y^{90} implanted experimental animals over the control animals was achieved.—*David Morse, M.D.*

Kirkland, Keith. Urological aspects of hydatid disease. *Brit. J. Urol.*, June, 1966, *38*, 241–254. (From: Sydney Hospital, Sydney, N. S. W., Australia.)

Two species of Echinococcus have a human relationship in hydatid disease, *E. granulosus* and *E.*

multilocularis, the former occurring more generally.

Dogs, wolves, jackals and hyenas are common primary hosts and the domestic intermediate hosts are sheep, cattle and pigs (excluding man). The worms lie deeply in the mucosa of the small intestine of the primary host, shed many hundreds of ova which, after ingestion by the intermediate host, lose their chitinous capsule, and as embryos penetrate the bowel wall to enter the portal venous system and most commonly become arrested in the capillary beds of the liver and lungs. Primary infestation of the genitourinary tract results in cyst formation at the site of arrest, invariably in the kidney, which comprises about 2 per cent of the human cases. Most primary renal infestations are single.

Each cyst has 3 layers, the endocyst and ectocyst of the parasite, which are surrounded by the adventitia or pericyst formed by the host. Secondary spread occurs following rupture of the primary cyst with discharge of scolices and daughter cysts, each of which can adapt itself to a new environment, if arrested before passing out of the body. Secondary spread to the genitourinary tract is commonly from the liver, spleen, mesentery, or muscles adjacent to the peritoneal cavity.

For diagnosis of primary hydatidosis, the roentgen examination is most important. Because many hydatid cysts may have no characteristic features, the plane roentgenogram often is of limited value. Large masses with thin rims of calcification may occur with hydatid disease, but this same appearance has also been seen with polycystic kidney and hypernephroma. Pyelographic findings have been described by Surraco and Mezzera as cup, claw, or bunch of grapes signs, but again these signs are not specific.

A history of previous hydatic disease, presence of a tumor, positive serologic tests, and calcification of the tumor mass are factors in diagnosis of secondary infestation.

The treatment of this disease is surgical and because of the invasive nature of the parasite, nephrectomy would appear to be always indicated in renal involvement.—*James R. Knapp, M.D.*

SIMPSON, ALAN, and ASHBY, EDWIN C. Anuria due to ureteric obstruction by blood clot. *Brit. J. Urol.*, April, 1966, *38*, 177–181. (From: The Royal Hospital, Sheffield, England.)

Three detailed case histories of anuria secondary to ureteric obstruction by blood clots are presented. The clots resulted from injury, renal papillary necrosis, and hypernephroma. Two of the cases were found to have only one kidney.

The authors point out that complete anuria is nearly always of obstructive origin. When the obstruction cannot be relieved by ureteric catheter irrigation, ureterostomy should be done. If the clot is secondary to renal papillary necrosis, catheter lavage might be considered for 7 to 10 days before resorting to ureterostomy.—*George A. Miller, M.D.*

DOWNS, RALPH A., and ROGERS, PAUL L. The voiding cystourethrogram in the evaluation of women with recurrent or chronic bladder symptoms. *South. M. J.*, June, 1966, *59*, 656–661. (From: Departments of Radiology and Urology, St. Edwards Mercy Hospital, Fort Smith, Ark.)

The authors review briefly the history of voiding cystourethrography, and discuss their technique. The bladder is filled with a catheter, and fluoroscopic and spot roentgenographic studies are made. They prefer an image amplifier, but indicate that this is not a necessity. A series of 12–14 spot roentgenograms are made during the act of urination.

Roentgenographic reproductious are included, illustrating distal urethrostenosis, bladder neck contractures, urethral diverticula, and ureteral reflux.

The differential diagnosis of these conditions is discussed.—*George L. Sackett, Jr., M.D.*

ESQUIVAL, A., CHILDE, A. E., and CUMMING, G. R. Urographic anomalies in congenital heart disease. *J. Canad. A. Radiologists*, June, 1966, *17*, 97–102. (From: Departments of Pediatrics and Radiology, Children's Hospital, Winnipeg, Manitoba, Canada.)

A long standing impression exists in medicine that patients with a known congenital anomaly are more likely to have additional anomalies than the general population. To study the incidence of anomalies of the renal system in patients with congenital heart disease, 628 patients, 414 of whom had congenital heart disease, were routinely evaluated with a post-angiographic roentgen survey of the abdomen.

Numerous postmortem studies indicate that approximately 10 per cent of the general population bears one or more anomalies of the genitourinary system. Results obtained in this study indicate an incidence of 26.9 per cent in patients with ventricular septal defects; however, in those patients with other forms of congenital or acquired heart disease the incidence falls within the expected range for the general population.

Thus it would appear that with the exception of patients with ventricular septal defects, renal anomalies occur in patients with congenital heart disease with the same frequency as in the general population. However, this rate of incidence renders routine abdominal roentgen evaluation following angiographic studies worthy of general use.—*Frederick R. Cushing, M.D.*

CHAWLA, S., BERY, K., and INDRA, K. J. Abnormalities of urinary tract and skeleton associated with congenital absence of vagina.

Brit. M. J., June 4, 1966, *1*, 1398–1400. (From: Radiology Department, Lady Hardinge Medical College and Hospital, New Delhi, India.)

Twenty-three cases of congenital absence of the vagina are tabulated in which 11 were found to have various upper urinary tract anomalies, and 4 had some skeletal anomalies. With this high incidence of upper urinary tract malformation it seems mandatory to thoroughly investigate this aspect of the condition prior to any reconstructive surgery. An ectopic pelvic kidney could interfere and could be injured during the surgical procedure.

In reviewing the literature the authors describe numerous skeletal anomalies which are associated with this condition. These include: hip dislocations, malformations of the foot, arms and ribs, cervical spina bifida, hemivertebrae, and transitional vertebrae.

When skeletal anomalies are discovered in infants, the radiologist should alert his referring physicians to the possibility of co-existent genitourinary anomalies. —*Arch H. Hall, M.D.*

Wolfromm, R., Dehouve, A., Degand, F., Wattez, E., Lange, R., Crehalet, A., and members of the Société de Radiologie. Les accidents graves par injection intraveineuse de substances iodées pour urographie: rapport général. (Grave accidents from the intravenous injection of iodized substances for urography: general report.) *J. de radiol., d'électrol. et de méd. nucléaire*, June–July, 1966, *47*, 346–357.

La Société de Radiologie surveyed its members for their experiences with the intravenous injection of iodized solutions and found that there had been 15 deaths and 166 grave accidents in 912,300 urographies. This is a death rate of 1/60,820, and an accident rate of 1/2,850. Most cases exhibited evidence of cardiovascular collapse.

Seventy per cent of the reporting radiologists used test doses as prophylaxis; 28 per cent systematically used prophylactic treatment (of which 82 per cent used antihistamines and 18 per cent corticoids).

For treatment of a severe reaction the choices were corticoids, antihistamines, oxygen and cardiac stimulants, in that order. Intravenous fluids are indicated to stimulate excretion of the drug, which takes longer than is often thought. This depends on the medium used and the dose; for example, it takes 120 minutes to eliminate via the urine 50 per cent of a 15 gm. dose of hypaque.—*Frank A. Riebel, M.D.*

Moorhead, Edward L., II, Caldwell, John R., Kelly, Annetta R., and Morales, Azorides R. The diagnosis of pheochromocytoma: analysis of 26 cases. *J.A.M.A.*, June 27, 1966, *196*, 1107–1113. (From: Medical Division No. 6, Division of Hypertension, and the Department of Laboratories, Henry Ford Hospital, Detroit, Mich.)

In an analysis of 26 cases of pheochromocytoma seen at the Henry Ford Hospital, the presenting complaint often seemed to be unrelated to the presence of pheochromocytoma; only 50 per cent gave a history of hypertension. This tumor is called one of the "great imitators." It has been known to mimic malignant hypertension, hyperthyroidism, coronary artery disease, causes of severe headache, etc. Despite the availability of both the histamine and phentolamine (regitine) screening tests, the diagnosis is still often made only at the autopsy table.

Untreated patients have a high mortality and it is suggested that one of the screening tests be part of the work-up of every patient with hypertension prior to initiation of therapy. Positive screening tests or presence of a highly suggestive clinical picture require analysis of the urine for catecholamines.

Although the presenting complaint often seemed unrelated to the presence of a tumor, the complete history disclosed symptoms and signs often associated with pheochromocytoma. Tabulated physical findings and presenting complaints reveal that 77 per cent had hypertension, 78 per cent had abnormal electrocardiograms, 42 per cent had paroxyms of one kind or another, 12 per cent had an abdominal mass and 31 per cent had retinal angiopathy.

Routine laboratory studies and roentgenologic examinations are rarely of value. Ninety-three per cent of the phentolamine (regitine) tests were positive and 78 per cent of the histamine tests were positive.

This is a rare tumor which occurred once in 23,809 patient registrations at Henry Ford Hospital. It is conceivable that as many as 1,000 cases occur annually in the United States.—*Richard E. Kinzer, M.D.*

Pisapia, M. I tumori corticosurrenali funzionanti: considerazioni su un caso di adenoma virilizzante. (Functioning adrenal cortical tumors: report of a case of virilizing adenoma.) *Nuntius Radiol.*, Oct., 1965, *31*, 1091–1106. (From: Istituto di Radiologia Medica dell'Università di Roma, Rome, Italy.)

A case of virilizing adenoma of the adrenal cortex, observed in a woman of 30 years of age, is reported.

The patient at the time of admission showed all the characteristic clinical and laboratory findings and symptoms.

A roentgen study of the kidneys and adrenals by retroperitoneal air insufflation associated with intravenous urography demonstrated a rather large rounded mass apparently arising from the upper pole of the left kidney.

At surgery, a large adrenal tumor, weighing 500gm.,

was removed. Histologically, it proved to be a benign adenoma of the adrenal cortex.

Discussed at length are the hormonal changes and the histologic findings.—*A. F. Govoni, M.D.*

Nervous System

Martin, P., Lecomte, P., Paschetta, Ch., Sarrazin and Ollier. Myéloencéphalographie par moyens de contrastes opaques. (Myeloencephalography by means of opaque contrast media.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1966, *47*, 197–206. (From: Service de Neurologie et Service Central de Radiologie du Centre Hospitalier de Nice, Nice, France.)

"Extra fluid" lipiodol is the contrast agent used in myeloencephalography. This gives a sharp and clearly defined shadow, and readily delineates adjacent structures. The technique of examination is simple and dispenses with tomography, the complicated manipulations of a sick patient, and no anesthesia is required. The use of such agents is innocuous.

In large quantities the contrast medium can obscure details of adjacent structures, whereas smaller quantities produce a thin layer, ideal for such an examination.

The authors prefer the opaque contrast material to air or gas. The only disadvantage is the difficulty encountered, at times, in its removal at the end of the examination. Water soluble contrast agents would be ideal were it not for the extreme irritant action they have on tissues with which they come in contact.

The patient is placed on a tilt table, in the decubitus position, and the chest is supported by a cushion, with slight extension of the head. An amount of 5 to 10 cc. of lipiodol "extra fluid" is injected through a suboccipital or cisternal puncture. By changing the position of the table, the column of contrast material is made to flow in both directions, giving an excellent cervical myelogram as well as a posterior fossa encephalogram.

Films are exposed in the frontal and lateral projections, including the region of the cervical spine and the posterior fossa.

The authors make a plea for increased interest in and use of the opaque contrast media in myeloencephalography.

Thirty myeloencephalographic reproductions accompany this article, illustrating the normal and abnormal findings encountered during such an examination.—*William H. Shehadi, M.D.*

Skeletal System

Bowman, J. R., Piston, Robert E., and Meeks, Edwin A. (Johnson City, Tenn.) Infantile cortical hyperostosis—an allergic disease? *South. M. J.*, July, 1966, *59*, 795–800.

Following a discussion of the clinical course, roentgenographic features, and pathologic criteria of infantile cortical hyperostosis, the authors report 4 patients whose controlled clinical course would indicate that the disease is caused by allergens found within milk. In each, the diagnosis was established clinically and this was supplemented by roentgenographic diagnosis in 2 of these patients. Upon establishment of this diagnosis, milk was withdrawn from the diet and a clinical remission promptly ensued. Reintroduction of milk led to reappearance of signs and symptoms and, in 1 patient, of the roentgenographic criteria.

Additional indirect support is provided by the high index of allergic diseases found within the family background of the patients. Interestingly, each patient developed other allergic diseases as he grew older. Lastly, in no patient thus far studied has an infective agent been isolated.

These data would indicate that allergens found within milk, in some undefined way, establish an inflammatory response in and about selective periosteal sites. The healing of this periosteal reaction results in the disease infantile cortical hyperostosis.—*Frederick R. Cushing, M.D.*

Kettelkamp, Donald B., Campbell, Crawford J., and Bonfiglio, Michael. Dysplasia epiphysealis hemimelica: a report of fifteen cases and a review of the literature. *J. Bone & Joint Surg.*, June, 1966, *48-A*, 746–766. (From: Albany Medical College, Albany, N. Y., and State University of Iowa, Iowa City, Iowa.)

This developmental disorder is usually limited to either the medial or lateral half of a single extremity with asymmetric overgrowth of cartilage from the epiphysis or a tarsal or carpal bone with associated enchondral ossification. Perhaps a better name would be epiphyseal (or tarsal or carpal) osteochondroma which describes and locates the lesion. The patients are usually between 2 and 14 years of age. In 6 patients first diagnosed in adult life, 5 had rapid increase in size but there was no histologic or clinical evidence of malignancy. The exostoses characteristically develop on one side of a limb and two-thirds of the cases had multiple lesions. In 2 of the present cases, the entire epiphysis was involved by bony overgrowth. The medial side was affected twice as often as the lateral in the lower extremity and in the upper extremity the abnormality has been most frequently reported on the radial side. The most common sites are the talus and the distal femoral and tibial epiphyses. There may be abnormalities of the adjoining metaphyses.

The patients have pain, deformity and limited

motion depending somewhat upon the size and location of the osteochondromata. The deformity tends to increase with growth and the size of the lesion increases in proportion to the growth of normal bone.

The roentgenographic findings are: an irregular exostosis protruding from the epiphysis or tarsal or carpal bone usually eccentric in location. In the early stages there may only be an irregular enlargement of one side of the primary ossification center or a multicentric opacity adjacent to the bone. The ossification centers of affected bone usually appear prematurely. The microscopic study is that of an osteocartilagenous exostosis. In the mature lesions, the cartilage is diminished in amount and activity.

The authors present the details and line drawings of 15 new cases and review 42 cases previously reported in the literature. There are also multiple roentgenographic reproductions illustrating various stages in the development of these lesions. The location of the exostoses is mainly in the lower extremity. Five of their 15 cases had more than one bone involved. One 4 year old male had progressive overgrowth in length of the affected leg and had exostoses involving the femoral capital epiphysis, the distal femoral epiphysis medially, the proximal tibial epiphysis laterally, the distal tibial epiphysis medially, and the talus and navicular bone.

Treatment depends upon the amount of deformity and pain; improvement followed excision of all or a part of the lesion in 12 patients.—*M. E. Mottram, M.D.*

Trenta, A., Ciuccarelli, C., Moretti, S., and Mattii, M. Considerazioni clinico-radiologiche sull'osteopecilia; presentazione di tre casi. (Clinical and radiologic considerations on osteopoikilosis; report of 3 cases.) *Ann. radiol. diag.*, 1966, *38*, 515–537. (From: Istituto Ortopedico Rizzoli dell'Università di Bologna and Istituti di Radiologia e del Radio, Bologna, Italy.)

Three cases of osteopoikilosis are reported, 2 of which showed a familial trait.

Reviewed are the most accepted hypotheses on the etiology of osteopoikilosis, and discussed is its relationship with disseminated lenticular dermatosis.

It is thought that this association could be produced by a pathologic disorder involving both bone and connective tissue because of their common mesenchymal origin.—*A. F. Govoni, M.D.*

York, Samuel E., and Yendt, Edmund R. Osteomalacia associated with renal bicarbonate loss. *Canad. M. A. J.*, June 25, 1966, *94*, 1329–1342. (From: Department of Medicine, University of Toronto, and the Farquharson Investigation Unit, Toronto General Hospital, Toronto, Ontario, Canada.)

Severe osteomalacia with multiple fractures was observed in a woman with a dietary history of vitamin D deficiency and a decrease in plasma bicarbonate level.

At the age of 27, this 44 year old woman had been given roentgen therapy to the pelvic area for uterine fibroids and had had no further menstrual periods. This was followed by alternating constipation and diarrhea, epigastric fullness after meals, dull epigastric pain and thirst. At the age of 37, the patient began having bone pain and finally, at the age of 42, she was confined to wheel chair.

Roentgenographic studies showed thinning of the bone cortex, and healing fractures of the right ulna and of the left ulna.

The serum calcium was 8.9 mg./100 ml. and the serum phosphorus 2.5 mg./100 ml.

At the first admission in May 1962, at the age of 44, there was persistent lowering of plasma bicarbonate levels which ranged between 17 and 19 mM./l. At this time there were pseudofractures of scapulæ, pubic rami, and other bones. The serum alkaline phosphatase was elevated to 30 to 42 King-Armstrong units. The serum calcium levels were 8.7 to 8.9 mg./100 ml. and the serum phosphorous 2.1 to 2.8 mg./100 ml., with the serum phosphorous rising to 3.2 to 3.3 mg./100 ml. after 3 weeks on a normal diet without medication.

Diagnosis of osteomalacia was made by bone biopsy, the roentgenographic evidence of decreased bone density and multiple pseudofractures, and by the elevated serum phosphatase levels. Rapid symptomatic improvement occurred after vitamin D administration and correction of the acidosis with sodium bicarbonate.

The possibility that the osteomalacia in this patient may have been due to chronic metabolic acidosis is discussed.—*Richard E. Kinzer, M.D.*

Persson, Björn M. Synovial osteochondromatosis of the hip: report of 8 cases including 2 in brothers. *Acta orthop. scandinav.*, 1966, *37*, 88–96. (From: Orthopaedic Clinic, Lund, Sweden.)

The author reports 8 cases of osteochondromatosis occurring in the hip joints, seen over a 20 year period. He discusses the incidence and appearance of this disease. Two of the cases occurred in brothers.

In several of the cases the development of the calcified bodies over a period of time was observed.—*George L. Sackett, Jr., M.D.*

Sutro, Charles J. The big toe: comparative anatomic and radiographic study of the metatarso-phalangeal articulation. *Bull. Hosp. Joint Dis.*, Oct., 1965, *26*, 141–174.

The author studied 100 big toes, removed at postmortem examinations or from amputated limbs, by histologic and roentgenographic methods.

The purpose of this work was to correlate the roentgenographic, gross pathologic and microscopic changes of the bones at the metatarso-phalangeal articulation.

It was found that the big toe showed certain features when hallux valgus was present. The plantar aspect of the metatarsal head was projected in such a fashion that a rounded bony mass was formed on the medial aspect of the metatarsal head and neck. Many of these big toes revealed cystic changes involving the metatarsal head and neck. These cystic areas consisted of foci of fibrous tissue and were the result of bone reabsorption at the site of ligamentous attachment. In the case of hallux valgus these cystic areas were of non-rheumatoid or of non-infectious origin.

Degenerative osteoarthritis was common in the metatarsal phalangeal sesamoid complex in both neutral and in valgoid-deviated proximal phalanges. Osteophyte formations involving the sesamoids were much more common in the non-valgoid toes. Osteophytes were common on the base of the proximal phalanx.

Another common finding was a depression in the articular surface of the tibial side of the metatarsal head. This was thought to be initiated by the rim of the base of the proximal phalanx.—*Richard P. Taylor, M.D.*

KAMBIN, PARVIZ. Giant-cell tumor of the thoracic spine with pathological fracture and paraparesis: a method of stabilization; a case report. *J. Bone & Joint Surg.*, June, 1966, *48-A*, 779–782. (Address: 1930 Chestnut Street, Philadelphia, Pa.)

Giant-cell tumor of the spine is rare and the diagnosis often challenged since many such lesions have proved to be aneurysmal bone cysts on review.

In the reported case the giant-cell tumor was located in the 12th thoracic vertebra in a female 23 years of age with a short history of pain and muscle spasm. Neurologic examination was negative. The roentgenograms showed an osteolytic lesion of the body and right pedicle of T12 with an adjacent soft tissue mass, which displaced the right 12th rib laterally. There was no evidence of calcification or new bone formation. At surgery, it was found that the mass surrounded the spinal cord. The histologic diagnosis was giant-cell tumor Grade II.

Since complete removal was impossible the patient was given approximately 3,000 r tumor dose with temporary improvement. However, within a short time she developed weakness and numbness in the lower extremities and T12 completely collapsed with subluxation on T11 necessitating decompression of the spinal cord. The section showed giant-cell tumor Grade II with hemorrhage and necrosis secondary to the radiation therapy. Harrington rods and fusion were used approximately 6 months later. The involved bone gradually recalcified and at 36 months the patient was asymptomatic.—*M. E. Mottram, M.D.*

AMSTUTZ, HARLAN C., and CAREY, EDWARD J. Skeletal manifestations and treatment of Gaucher's disease: review of twenty cases. *J. Bone & Joint Surg.*, June, 1966, *48-A*, 670–701. (Address: Dr. Amstutz, 535 East 70th Street, New York, N. Y.)

Twenty cases of Gaucher's disease, 13 with over a 10 year follow-up, are reviewed in detail. The diagnosis was usually established by demonstration of typical Gaucher's cells in the sternal marrow, spleen or bone. There was no consistent elevation of the serum acid phosphatase.

The presenting skeletal symptoms may appear at any age and are related to replacement of the bone marrow by Gaucher's cells with associated expansion and erosion of the cortex. Eventually, avascular necrosis or pathologic fracture may occur. Twelve patients complained of pain in the hip, knee, shoulder or spine and there usually was progressive joint degeneration especially in the hip. Eight patients with splenomegaly, fatigue or bleeding did not have skeletal symptoms initially but these developed later. In all patients, skeletal manifestations became more prominent with advancing age.

The femur was involved in all 20 patients and usually showed the earliest changes and produced the most skeletal disability. Roentgenograms showed areas of demineralization with the overlying cortex thin, eroded and expanded. There was usually an Erlenmeyer flask outline often with a vertical line of rarefaction adjacent to the linea aspera. The femoral shaft, particularly the metaphyses, occasionally showed a reticular pattern with irregular sclerosis. Seven patients had fracture of the proximal end of the femur and 4 failed to unite. Aseptic necrosis of the femoral head occurred in 15 of the 20 patients and was bilateral in 6 children and 3 adults. Healing occurred more rapidly in the younger patients. With progressive hip changes the joint space eventually narrowed, reactive bone formed and in some there was complete disintegration of the joint. In 1 patient the femoral head and acetabulum were destroyed within 18 months.

Skeletal changes similar to those in the femur occurred in other long bones and to a lesser extent in the short tubular bones. Three patients had necrosis of the humeral head; 2 bilaterally. One had necrosis of the radial head and another of the talus. Radiolucent areas were also noted in the mandible and skull. Pathologic vertebral compressions occurred in 3 patients.

Two patients developed clinical and roentgenographic changes indistinguishable from osteomyelitis; this appears to be self-limited with the symptoms lasting 1 to 4 weeks. There was periosteal reaction

along the shaft and 1 patient had diffuse mottled rarefaction in the underlying bone. Secondary infection may occur as a result of bacteremia or contamination by aspiration.

Splenectomy in 6 patients did not influence the onset or progression of the skeletal changes. Roentgen therapy in small to moderate amounts relieved pain in 4 of 7 patients and 2 had deleterious results but because of the variability in the course of the disease it is difficult to evaluate therapy. In treating necrosis of the femoral head in adults the early results of femoral head replacement with long-stem prostheses have been encouraging.—*M. E. Mottram, M.D.*

Marquès, P., Faillières, J., and Sancerni, M.-M. Les métastases osseuses du cancer du col utérin. (Osseous metastases from cancer of the uterine cervix.) *J. de radiol., d'électrol. et de méd. nucléaire*, June–July, 1966, *47*, 309–320. (From: Centre anticancéreux de Toulouse, France.)

Classically, cancers of the uterine cervix have not been considered to be osteophilic. The authors, however, in reporting 27 cases wherein metastases have reached bone suggest that this notion should be re-evaluated, since an incidence of 4 per cent appears to be significant.

The pelvis and lumbar spine are most commonly affected, but the authors also found lesions in the cervical and dorsal spine, calvarium, ribs, humerus and lower extremities. These are invariably osteolytic and never bone productive; the spread may be either hematogenous or by contiguity. Most frequent in advanced stages of the disease, they tend to be found in relatively younger patients. In no case did the discovery of a metastasis precede the finding of the primary source. In monostotic lesions a bone survey is indicated, since in the rare case one can hope for cure.

Radiation therapy is preferred for polyostotic lesions, the dose being 4,000 rads for roentgen, or 5,000 rads for cobalt 60 therapy.

Radioisotopes by internal administration do not appear to be practicable and chemotherapy is disappointing, but progesterone and testosterone given together have been palliative.—*Frank A. Riebel, M.D.*

Svane, Sivert. Ehlers-Danlos syndrome: a case with some skeletal changes. *Acta orthop. scandinav.*, 1966, *37*, 49–57. (From: Department of Surgery, Nordland County Hospital, Stokmarknes, Norway.)

Ehlers-Danlos syndrome is characterized by hyperelasticity of the skin, increased fragility of the skin and blood vessels and increased laxity and mobility of the joints.

A case of a 54 year old woman with Ehlers-Danlos syndrome is reported. She had bilateral hip dislocations, marked kyphoscoliosis, twisting of the leg bones and subluxation of several toe joints.

These patients frequently seek medical advice for skeletal deformities or recurrent joint dislocation.—*John H. Harris, M.D.*

Khoo, Tan Kheng, and Balachandran, N. Osteogenic sarcoma of soft tissues. *Singapore M. J.*, March, 1966, *7*, 30–33. (From: Department of Pathology, and Orthopaedic Surgery, General Hospital, Singapore.)

Because of the rarity of osteogenic sarcoma of soft tissue, another such case is reported. The lesion in this instance was in the soft tissue on the anterolateral border of the wrist and measured $2\frac{1}{2} \times 1\frac{1}{2}$ inches at operation. It was clearly demonstrated to have no connection with the bone or periosteum at the lower end of the radius.

The mass showed considerable calcification. The pathologic diagnosis was osteogenic sarcoma of soft tissue of the sclerotic type. The patient was first seen June 11, 1964, and has had two metastatic recurrences since.—*John H. Harris, M.D.*

Kinsella, T. Douglas, MacDonald, F. Robert, and Johnson, Louis G. Ankylosing spondylitis: a late re-evaluation of 92 cases. *Canad. M. A. J.*, July 2, 1966, *95*, 1–9. (Address: Dr. L. G. Johnson, Director, Division of Rheumatology, McGill University Clinic, Montreal, Quebec, Canada.)

A group of 92 patients who satisfied the criteria of the American Rheumatism Association for the diagnosis of ankylosing spondylitis were re-evaluated by the authors through the use of clinical, radiologic, and laboratory parameters. At the time of the study 72 patients were still alive. Of these, 50 had received therapeutic irradiation in an attempt to try to alter the clinical course of the disease. They were treated with 200 kvp. radiation having a half value layer of 1 mm. Cu, and using a focal skin distance of 50 cm. The patients received a total dose of 3,000 r to the spine in 3 series spread over a 9 to 12 month period of time. They received 1,000 r per series given over a 15 day period to 8 ports encompassing each sacroiliac joint, and separate lumbar, thoracic and cervical fields. Almost all the patients who could tolerate the initial radiation sickness experienced symptomatic relief of spinal arthralgia, which lasted on the average for 2 years. Following this, the symptoms recurred and the natural course of the disease progressed in an unaltered manner. The authors have abandoned the use of radiation therapy because of this finding and also because several of their patients developed leukemia and aplastic anemia.

An analysis of the total group revealed an 8 per cent incidence of aortic insufficiency, an 11 per cent incidence of iritis, a 3 per cent incidence of psoriasis,

and only 1 patient with regional enteritis. Approximately 50 per cent of the patients had objective evidence of peripheral joint involvement. No characteristic dysproteinemia was demonstrated and normal values for rheumatoid factor, antinuclear factor and antithyroglobulin were the rule.

The roentgenographic findings included an almost universal involvement of the sacroiliac joints. The second most common finding was anterior spondylitis especially in the region of T 11 to L 2. There was also a high rate of involvement of the posterior lumbar and costovertebral joints. Of the peripheral joints, the glenohumeral and the acromioclavicular joints were the most frequently involved.

The authors conclude by stating that they believe that it is unusual for ankylosing spondylitis to "burn out" spontaneously, or after irradiation, or other forms of therapy. They also believe that the currently accepted criteria for the diagnosis of ankylosing spondylitis, although useful, should be enlarged and refined.—*Kenneth M. Nowicki, M.D.*

Blood and Lymph System

Nowicki, Georges. (Cracovie, Poland.) Calcification des artères du bouquet aortique. (Calcification of the arteries of the aortic bouquet.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1966, *47*, 217–222.

Calcification of the arteries of the aortic bouquet (branches of the arch of the aorta) is a very rare condition and has been observed only once in 68,724 patients examined by the author. A review of the available literature fails to disclose any report of such a case.

Visualization of the vessels arising from the aortic arch with the plain roentgenogram practically never occurs. Pathologic conditions involving these vessels, without calcification in their walls, are likewise not demonstrable on routine roentgenographic examinations.

The author reports the case of a 63 year old female who was hospitalized at the Internal Medicine Service (Cracovie, Poland), in August, 1960, because of increasing morning cough and expectoration, poor general health, and loss of weight.

Roentgenographic examination of the chest revealed changes at the right base, interpreted as pulmonary and peribronchial fibrosis, and probable bronchiectasis.

The heart was within normal limits. The aortic arch was elongated and tortuous. There was considerable diffuse calcification of the entire thoracic aorta. Definite calcification, however, was identified along the course of the innominate, subclavian and common carotid arteries. While this was identified on the plain roentgenogram, the sharp delineation and contrast of these calcified vessels with the surrounding clear lung structure was enhanced by tomography.

The author stresses the fact that there was nothing in the patient's clinical history or physical findings that would indicate the presence of calcification of these vessels. The physical examination failed to reveal any alteration of pulse pressure or retardation of the radial pulse. The diagnosis could only be made by roentgenographic examination, which clearly outlined the calcified vessels arising from the arch of the aorta—the innominate artery and its branches, the right subclavian and the right common carotid artery, the left common carotid artery, and the left subclavian artery.

The author proposes the term "calcinosis arteriarum arcus aortae." To the best of his knowledge such an entity has not been previously described.

Seven illustrative roentgenographic reproductions accompany this presentation.—*William H. Shehadi, M.D.*

Benchimol, Alberto, and McNally, Edward M. Hemodynamic and electrocardiographic effects of selective coronary angiography in man. *New England J. Med.*, June 2, 1966, *274*, 1217–1224. (From: Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, La Jolla, Calif.)

The hemodynamic consequences of selective coronary angiography were studied in 29 patients, 18 of whom had significant coronary occlusive disease according to angiographic criteria.

Injection of 5 cc. of hypaque into either coronary artery caused immediate sinus bradycardia, "ischemic" electrocardiographic changes, and significant decreases in coronary artery and systemic blood pressures. All changes subsided within 1 minute of injection. The responses of normal and diseased patients were identical.

No major complications occurred in any of the 29 patients included in this study, although 4 major but nonfatal complications had been encountered during the authors' total experience with 81 cases. Of 3 instances of ventricular fibrillation, 2 were related to mechanical effects of the catheter rather than to injection of the contrast agent. Myocardial infarction followed angiography in 1 patient with preinfarction angina. The patient made an uneventful recovery.—*Rosalind H. Troupin, M.D.*

Vuorinen, P. Results of thoracic aortography in examination of the brachiocephalic circulation: report of a series of 102 aortographies. *Radiol. clin. et biol.*, 1965, *34*, 377–385. (From: Radiological Department, University Central Hospital, Turku, Finland.)

A total of 102 thoracic aortographies was performed during the years 1962–1964. A modified Seldinger percutaneous catheterization technique was employed, with the group almost equally divided

between axillary and femoral approaches. No complications were recorded and no comment is offered regarding the relative merits of the two routes.

The type and distribution of abnormalities parallel previous experience in the literature. Atherosclerotic stenoses typically were found at the branch origins.

Four case reports of "subclavian steal syndrome" are included and there are 2 case reports of congenital arteriovenous fistula between the right subclavian artery and the azygos vein.—*Rosalind H. Troupin, M.D.*

Viville, Ch., Gillet, M., and Reins, R. Les complications de l'aortographie lombaire (ou aortographie directe) et leur prévention. (The complications of lumbar aortography [or direct aortography] and their prevention.) *J. de radiol., d'électrol. et de méd. nucléaire*, June–July, 1966, *47*, 289–308. (From: Clinique chirurgicale B., C. H. V. of Strasbourg, France.)

Lumbar aortography remains an indispensable method of investigation, particularly for arteritis of the lower extremities. Since, however, it carries a 1 to 300 expectation of death or grave complication it should be reserved for those cases in which the Seldinger technique is impracticable.

These adverse results can be minimized by the avoidance of: (1) intramural injection (especially likely with a beveled needle), (2) too large a dose of opaque media, (3) use of too great a pressure, (4) repeated injections, (5) poor selection of patients, and (6) injection at a dangerous level.

The authors are impressed with the great variety of untoward results which have been reported, among them infections, gas emboli, allergic phenomena, osseous damage, acute pancreatitis, suprarenal necrosis, and deaths from injecting a pheochromocytoma. One of the authors' cases was unusual in that there was disco-vertebral necrosis at L1–L2.

The patient should be well hydrated before surgery, and receive careful postoperative surveillance. The *clinical* signs of alarm are pain, oliguria, albuminuria, hematuria, drop in arterial pressure or modification of reflexes. The *radiological* signs of alarm are: (1) intramural injection (preventable by making a small injection first to confirm the position of the needle, which also constitutes a test dose for sensitivity), (2) massive or preferential dose in one arterial branch, and (3) mottled, irregular, or persistent nephrogram. The latter is so important that additional filming is advised about 5 minutes after the injection.—*Frank A. Riebel, M.D.*

Sarkany, I., and Kreel, L. Subcutaneous ossification of the legs in chronic venous stasis. *Brit. M. J.*, July 2, 1966, *2*, 27–28. (From: Royal Free Hospital, London, England.)

The authors report 8 patients with subcutaneous ossification of the legs and present a brief review of the important clinical, roentgenologic and pathologic features.

Subcutaneous ossification of the legs associated with chronic venous stasis is not a well-known entity. This ossification may be seen with or without a nonhealing ulcer. It was previously reported to have occurred only in postmenopausal females with chronic venous stasis and co-existing fungal infections of the feet. The authors report the first case in a male.

These subcutaneous ossifications have a pathognomonic picture. The bone formation is confined to the subcutaneous layer and produces a coarse network of opacities of bone density in the lower leg. This specific roentgenographic change makes a definite diagnosis possible without recourse to a complicated medical investigation.—*Richard P. Taylor, M.D.*

Godart, S. Embryological significance of lymphangioma. *Arch. Dis. Childhood*, April, 1966, *41*, 204–206. (From: Service de Chirurgie Infantile et d'Orthopédie à l'Hôpital Universitaire Brugmann, Bruxelles, Belgium.)

Lymphatic vessels do not generate by centrifugal growth from veins and lymph cavities, as has long been believed. At a very early stage (9 to 12 mm.) of fetal development, mesenchymal slits appear in the reticulum of a rich venous plexus. By coalescence of these spaces, large lymphatic cavities are formed which open secondarily into the venous system. Later, they decrease in size and straighten out following the direction of the veins.

Should the primary lymphatic spaces fail to join the central system, cyst formation is induced. The lack of communication between a lymphatic sac and the venous system produces a cystic hygroma. This is the reason why cystic hygromas are found in the same locations as fetal lymphatic sacs, namely, cervical, mediastinal, or retroperitoneal.

In cavernous lymphangioma the sequestration is more peripheral than in cystic hygroma: primary lymphatic spaces do not join the main central collectors. Lymphangioma simplex is the result of a still more localized sequestration of a few mesenchymal slits.

Tumor growth occurs through accumulation of peripheral lymph trapped in the central cavities, secondary to atresia of the main collectors.—*Donald M. Monson, M.D.*

Chiappa, S., Uslenghi, C., Bonadonna, G., Marano, P., and Ravasi, G. Combined testicular and foot lymphangiography in testicular carcinomas. *Surg., Gynec. & Obst.*, July, 1966, *123*, 1–14. (From: Istituto di Radiologia, Università di Milano and Isti-

tuto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy.)

This article is the result of the authors' experience in performing lymphangiography in 36 patients with testicular tumors.

In one group of patients, testicular lymphangiography was performed first; a few days later, foot lymphangiography was carried out. In a second group of patients, foot lymphangiography was performed first; this was followed by testicular lymphangiography. Another group of patients received only foot lymphangiography. The fourth group of patients only had testicular lymphangiography.

The purpose of this work was to determine whether or not "the specific testicular lymph center" belonged to the para-aortic lymph node chain.

It was found that only after the specific testicular lymph node center filled would the para-aortic lymph nodes fill. This specific lymph node center did not visualize after foot lymphangiography.

The authors conclude that testicular lymphangiography is particularly indicated to detect early lymph node metastases, whereas foot lymphangiography is of value to demonstrate para-aortic lymph node involvement.—*Richard P. Taylor, M.D.*

RADIATION THERAPY

D'Angio, G. J. Soft-tissue sarcomas of the nasopharynx and orbit in children. *Proc. Roy. Soc. Med.*, May, 1966, *59*, 412–413. (From: University of Minnesota Hospitals, Minneapolis, Minn.)

The presenting complaints for nasopharyngeal soft tissue sarcoma are nasal stuffiness or nasal voice. The differential diagnosis includes: juvenile angiofibroma, carcinoma, lymphosarcoma and soft-tissue sarcomas. The roentgenologic survey should include roentgenograms of the chest and skeleton since these tumors often metastasize early to lungs and bones. It has been shown that nasopharyngography most clearly defines the lesion.

Because these tumors are inaccessible to radical removal by surgery, radiotherapy is the treatment of choice and cures can be effected. Supervoltage or cobalt 60 teletherapy is given with the aim of delivering a midline dose of 4,000 to 6,000 rads over a 4–6 week period. The specific dose level is selected on the basis of histologic evaluation and the age of the child. Intravenous actinomycin D is administered simultaneously with radiotherapy.

For the rapid growing orbital soft tissue sarcomas the usual presenting complaint is displacement of the globe. In addition to these tumors, the most common causes of proptosis in a child are hemangioma, optic nerve glioma, retinoblastoma, "histiocytosis X," lymphoma and metastatic tumor, especially neuroblastoma. It is noteworthy that these neoplasms tend to remain localized. The therapy of choice is exenteration of the orbital contents with radiation therapy given postoperatively when the surgical specimen shows doubtful margins or incomplete removal.—*Lionel W. Young, M.D.*

Williams, D. Innes. Rhabdomyosarcoma of the genito-urinary tract. *Proc. Roy. Soc. Med.*, May, 1966, *59*, 413–414. (From: The Hospital for Sick Children, Great Ormond Street, London, England.)

These tumors occur mainly in the first 3 or 4 years of life. The tumors originate in the submucosal layers of the bladder and may extend down the urethra, through the membranous portion of the male, and for the whole length of the female urethra. The lobulated form of this tumor within the bladder gives rise to strangury, a very severe desire to micturate without being able to accomplish it. Because of this, acute or subacute retention is frequently a presenting symptom and is accompanied by a great amount of pain. The obstruction leads to upper tract dilatation and to uremia and as a result symptoms of renal failure are present in some patients at the time of hospital admission.

Intravenous pyelogram may show a variable degree of obstruction. The ureters appear tense and full, not showing the tortuosity common in the congenital obstructions of childhood. Almost invariably there is a widening of the gap between the lower ends of the ureters where the tumor mass has separated them. In the bladder there appears a characteristic lobulated filling defect at its base or sometimes all over the bladder area. The posterior urethra may show a cone of dilatation maintained by the prolapsed lobules forcing their way down into the urethra. As a result the bladder neck appears wide. The urethra narrows somewhere around the verumontanum and the filling defect produced by lobules of tumor is observable. When there is renal failure, it is necessary to do injection cystograms to show the typical picture.

The diagnosis of rhabdomyosarcoma can be confirmed by cystoscopy and biopsy. The treatment of this tumor has been mainly by radical surgery.

Rhabdomyosarcoma of the prostate is characteristically a solid globular mass arising from the pelvis, displacing the bladder upwards and stretching the urethra over its surface. The common presenting symptoms are retention and infection. Roentgenologic examination once more shows upper tract dilatation with upper and forward displacement of the bladder. A good cystourethrogram may show the compression of the urethra. Because endoscopy is exceptionally difficult in these cases, a biopsy is best performed by a needle introduced from the perineum. Treatment is difficult and because of lack of success with limited resection, pelvic exenteration may be indicated in this condition.—*Lionel W. Young, M.D.*

Lee, E. Stanley. Rhabdomyosarcoma in adults. *Proc. Roy. Soc. Med.*, May, 1966, *59*, 414–415. (From: Westminster Hospital, London, England.)

Rhabdomyosarcoma is extremely rare in adults. At Westminster Hospital in London, in 7 years there have been 27 well-attested cases. These tumors fall into 2 groups: rhabdomyosarcomas of embryonal (childhood) type; and rhabdomyosarcomas of skeletal muscle masses.

The tumors in the former group are bulky, occurring in the mouth and pharynx, vulva and bladder, and perhaps the spermatic cord. These tumors are observed in young adults, and, because of this, it is suspected that they are a "hand-over" from the tumors of childhood possibly arising in some congenital anomaly or embryonal rest. Chemotherapy utilizing actinomycin D, and in some cases methotrexate, has been useful in reducing or prolonging tumor regressions.

The skeletal muscle rhabdomyosarcomas are a difficult group of tumors to distinguish from the larger group of soft tissue tumors in general. The age spread is wide and they may occur in any skeletal muscle. The speed of evolution varies from very slow to a hurricane swiftness. The mode of spread is unspecific and the prognosis equally variable. Treatment consists of surgical amputation or very wide excision with adequate radiotherapeutic cover.—*Lionel W. Young, M.D.*

Jelliffe, A. M. Hodgkin's disease. *Proc. Roy. Soc. Med.*, July, 1966, *59*, 605–607. (From: Meyerstein Institute of Radiotherapy, Middlesex Hospital, London, England.)

The term "early Hodgkin's disease" is used when it is thought that the disease is limited in its extent and when the prognosis appears to be relatively good. Although the disease varies considerably in its course, from patient to patient, it is possible to predict a less malignant course in some patients.

The author reports the experience at the Meyerstein Institute of Radiotherapy of the Middlesex Hospital with regard to the factors that influence the prognosis in Hodgkin's disease. These factors are: sex, where the prognosis is better in women; duration of disease which is difficult to assess accurately; stage of disease where early stages are associated with better survival; systemic manifestations where constitutional symptomatology is related to a poor prognosis; and microscopic appearances where better prognosis is associated with the paragranuloma and granuloma type lesions. However, one of the most important factors influencing the course of Hodgkin's disease is energetic radiotherapy in the early stages (Stage I and II).

The main problem remains one of deciding which patient has disease of the type that may be benefited enormously by energetic treatment and which patient has widespread disease unlikely to benefit.—*Luther W. Brady, M.D.*

Morson, Basil C. Factors influencing the prognosis of early cancer of the rectum. *Proc. Roy. Soc. Med.*, July, 1966, *59*, 607–608. (From: Pathology Department, St. Mark's Hospital, London, England.)

Early rectal cancer is defined as invasive carcinoma that has not spread in direct continuity beyond the submucous layer, regardless of the presence of blood-borne or lymphatic metastases. The author reports 2,305 rectal cancers admitted to St. Mark's Hospital between 1948 and 1962 with only 76 (3.3 per cent) in this category. This indicates that rectal cancer is rarely detected at an early stage in its natural history.

The author reviewed the incidence of carcinoma of the rectum according to Dukes classification A, B and C for each 5 year period in the years 1928 to 1962. The incidence of Dukes A cases remained approximately the same throughout this period at about 15 per cent of all cases. The incidence of Dukes B remained the same at 35 per cent and Dukes C at 50 per cent.

The author points out that although it appears that invasive cancer is coming to treatment no earlier today than in former times, there has been in recent years an apparent increase in the frequency with which rectal and colonic polyps are removed. This is largely due to greater skill in the detection of polyps by sigmoidoscopy and barium enema study, particularly the air contrast technique. Unfortunately, adenomatous polyps and villous tumors are often symptomless, being discovered by chance during examinations for symptoms due to other conditions.

Not all intestinal polyps are precancerous, but the removal of those that are should contribute towards the prevention of intestinal cancer.—*Luther W. Brady, M.D.*

Wallace, David M. Factors influencing the prognosis of early cancer of the bladder. *Proc. Roy. Soc. Med.*, July, 1966, *59*, 609–610. (From: St. Peter's Hospital and Royal Marsden Hospital, London, England.)

Some of the difficulties in understanding the behavior of bladder tumors is due to the confusion of pathologic nomenclature and the arbitrary division into benign and malignant types of growth. There is a scale of malignancy in bladder tumors but there does not yet appear to be a sharp partition between the two types. There are 2 main factors in prognosis: the surface extent of spread and the depth of infiltration, that is, stage. The bladder is not an anatomically nor physiologically water-tight organ but exists as a portion of the collecting system. Any disease affecting the bladder may affect any other component of the

urothelial system. Therefore, malignant tumors of the bladder may occur not only multifocally in space but also in time.

Staging has been recognized as a valid method of classification and the levels of staging especially in early disease are of particular importance. The basement membrane in the bladder is probably the greatest single factor in prognosis. Where the membrane has been ruptured, even with minimal breach, the mortality increases by 20 per cent and when there is spread into the submucosa proper of the bladder there is a further increase of 20 per cent. Superficial muscle infiltration causes a further increase, but as soon as the deep muscle or perivesical tissues are reached the incidence of positive lymph nodes increases rapidly to over 50 per cent of the bladders examined.

The author suggests that there may be one or more biochemical, environmental or social factors which initiate neoplasia. The crucial problem, however, is what causes one patient to grow tumors over many years without breaking the basement membrane and others to offer no resistance at all. He suggests that this may be related to a normal chromosomal count where no infiltration occurs, but, with a spread of the chromosome count, or where the count was of the 92–96 group, infiltration was almost always demonstrable.—*Luther W. Brady, M.D.*

TUDWAY, R. C. Factors which influence the prognosis of early tumors of the upper respiratory tract. *Proc. Roy. Soc. Med.*, July, 1966, *59*, 610–612. (From: Bristol General Hospital, Bristol, England.)

The prognosis in cases of tumors of the upper respiratory tract is determined by the same general factors which operate in all parts of the body. These are: the nature of the growth itself where the histologic nature of the tumor is the most important factor; the site of the growth whether it is accessible to treatment by surgery or radiotherapy; the early diagnosis and choice of treatment where diagnosis, while the lesion is still early, is vital for the choice of correct treatment; the local state of the tissues where local sepsis lowers the resistance of the tissues and favors the persistence or recurrence of growth, particularly when radiotherapy is used; and the general state of the patient where general debility adversely affects the prognosis by reducing the host resistance to the growth as well as by making adequate treatment more difficult or dangerous.

The author describes selected sites that should be considered in the light of the above factors influencing prognosis. These are: the vocal cord where early diagnosis is associated with excellent prognosis; the aryepiglottic fold where prognosis is 50–50 even when the growth is early and laryngectomy is performed at once; and the pyriform fossa where the growth is associated with a bad prognosis regardless of its extent.

It is suggested that the estimation of prognosis is difficult without all the detailed facts. Lesions of the upper respiratory tract are associated with variable prognoses and in some of the commonest types of growth, prognosis may be relatively good.—*Luther W. Brady, M.D.*

BENASSI, E., JULIANI, G., PICCOTTI, F., and ISOARDI PONS, A. Accrescimento di un duplice innesto del tumore di Ehrlich in forma solida—effetti della roentgenirradiazione di una sola localizzazione. (Rate of growth of double implants of the Ehrlich solid tumor; effects of the roentgen irradiation on one localization only.) *Radiol. med.*, Feb., 1966, *52*, 97–106. (From: Istituto di Radiologia dell'Università di Torino, Torino, Italy.)

Eighty-four albino Swiss male mice were inoculated with the ascitic type of Ehrlich's tumor, either in the right axilla and/or in the left groin.

This experimental study was conducted in order to establish: (1) whether the effects of localized irradiation of a neoplastic lesion are modified by the presence of a second similar but remote neoplastic growth, and (2) whether localized irradiation of one neoplastic implant might influence the rate of growth of a similar, remote neoplastic focus.

The technique of irradiation was: 230 kv., 12 ma., filter 5 mm. Al, half value layer of 0.20 mm. Cu, target skin distance of 27 cm., and a field of 2×2 cm. A dose of 3,000 r (air) was delivered in 1 treatment.

The results demonstrated: (1) that the irradiation of one of the implanted tumors did not significantly influence the rate of growth of the other implant, and (2) that the radiosensitivity of the treated tumor was somewhat increased by the presence of the remote growth.—*A. F. Govoni, M.D.*

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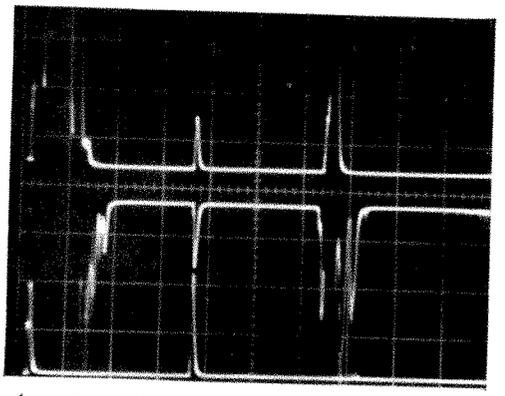
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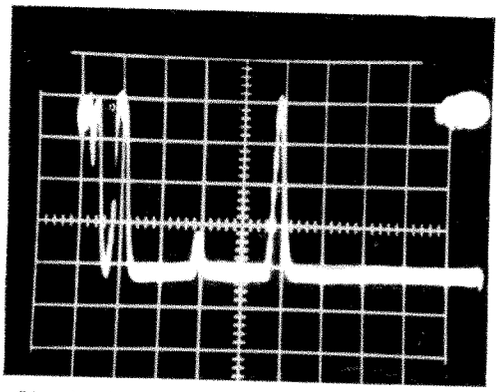
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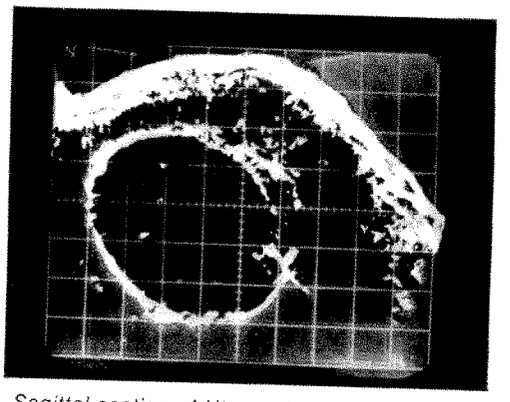


Location of Brain Midline

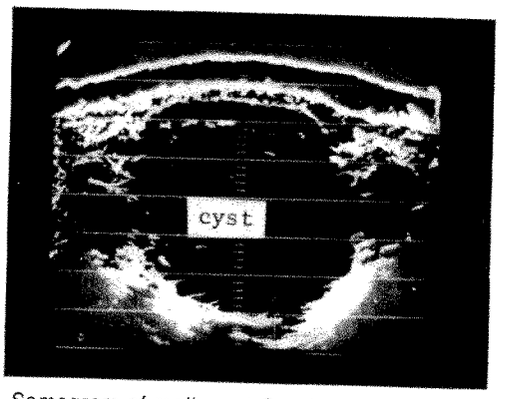


Biparietal diameter of Fetal Head. Ultrasonic measurement was 8.8 cm. Actual diameter at birth two days later was 9.0 cm.

VISUALIZATION
("B" scan)



Sagittal section of Uterus demonstrating Fetal Head.



Somagram of malignant Ovarian Cyst.

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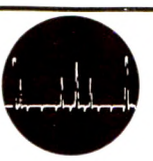
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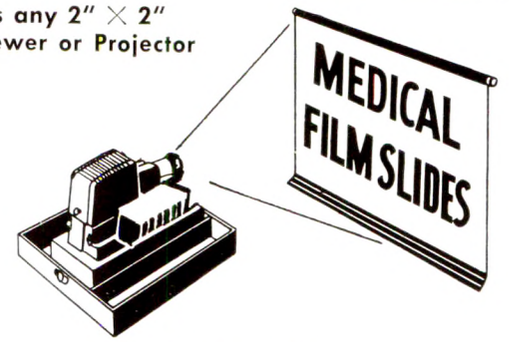
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'nopacification' is not a condition you can treat

determine the cause of nonopacification, most physicians rest re-examination. There are two ways this has been e by the oral route in the past:

y starting all over again at a later date — and sometimes oubling the dose of contrast agent on the second try;

y administering more contrast agent the evening of the rst unsuccessful examination (and, again, sometimes oubling the dose) and repeating the study the following ay.

n these methods share two inherent disadvantages. They a good deal of time, and they require the patient to a good deal of oral contrast agent. The amount given mes clinical importance because it has been reported er doses may result in considerable patient discomfort use of diarrhea and other significant side effects.[1]

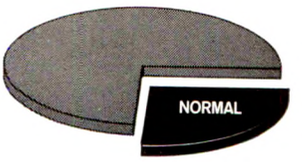
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grafin Calcium—absorbed so rapidly you can xamine the same day

e advantage of the calcium ipodate method is that the nination can be completed in five additional hours with nited dose of contrast agent."[1]

method is as productive as it is simple. If the initial ification is unsatisfactory, the patient is given 3 Gm. of calcium ipodate. Films are repeated 5 hours later. Here a the results of a recently published study on same day examination using Oragrafin Calcium:[1]

ANALYSIS OF ORAGRAFIN CALCIUM REENFORCEMENT
IN 76 CASES OF UNSATISFACTORY INITIAL OPACIFICATION



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Had the initial failure of opacification been assumed to b due to gallbladder disease, the 20 patients (26%) found normal by re-examination might have been erroneously diagnosed and might have undergone unnecessary surgery.

"Same day re-enforcement oral cholecystography utilizing calcium ipodate . . . is a rapid, accurate, low-dose method of obtaining additional information about a gallbladder which is unsatisfactorily opacified following routine cholecystography."[1]

There are other advantages to such rapid absorption. Even without prior preparation of the patient, both cholangiography and cholecystography can be performed on the same day. Optimal concentration in the hepatic and biliary ducts usually occurs within 1 to 3 hours. Although the gallbladder is optimally opacified approximately 10 hours after ingestion of Oragrafin, diagnostically valuable information can often be obtained within 5 hours or less.

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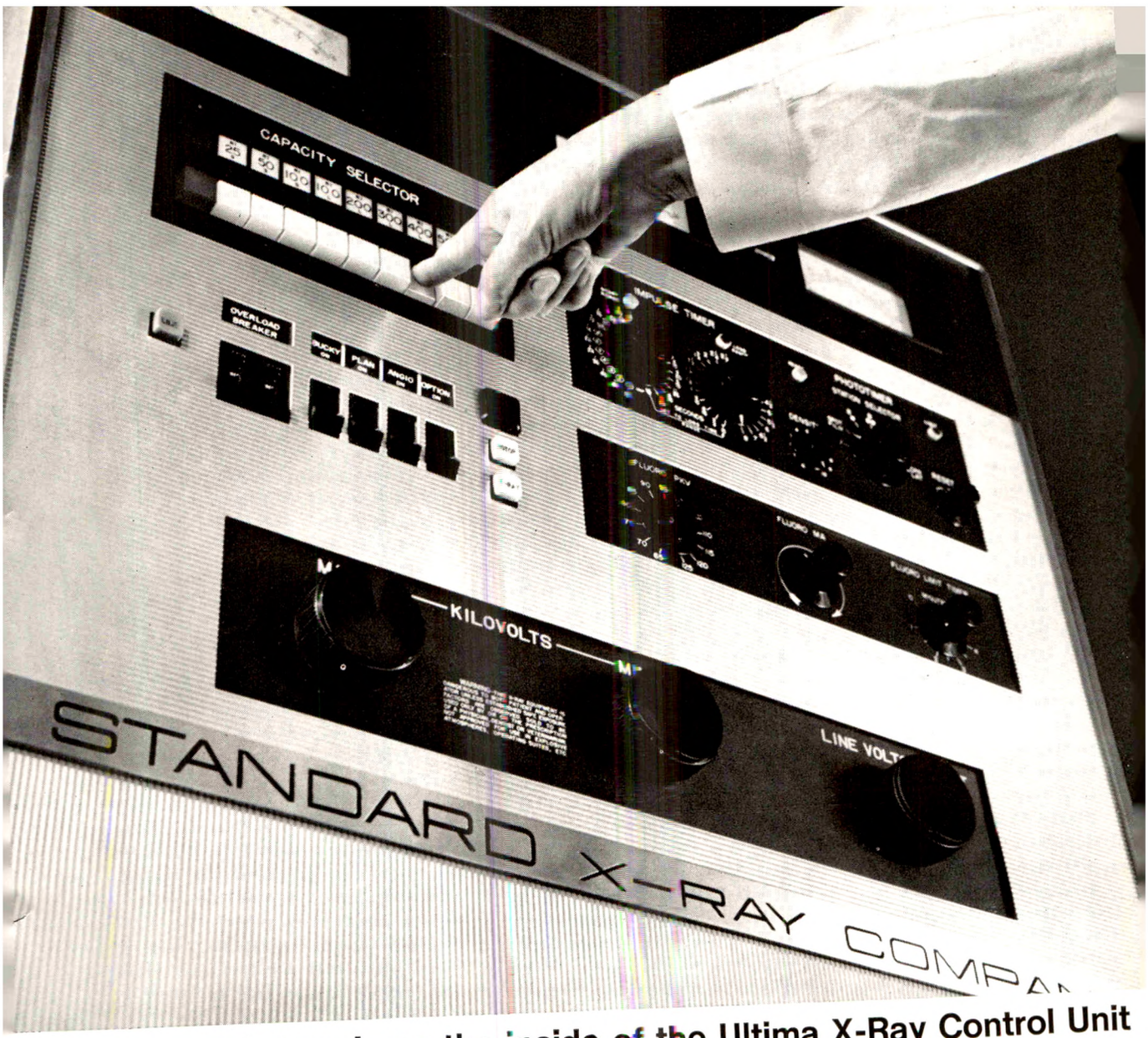
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Reference: 1. Crummy, A. B.: Wisconsin M. J.: 65:84, 1966.

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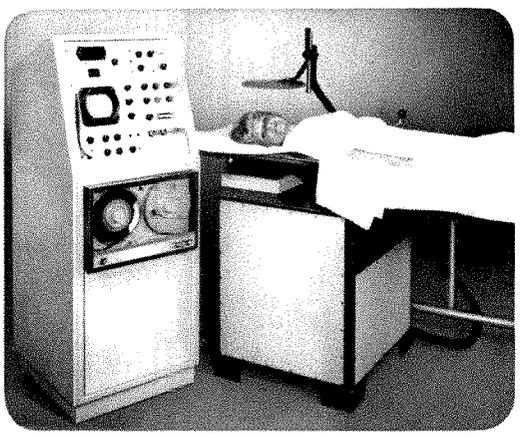
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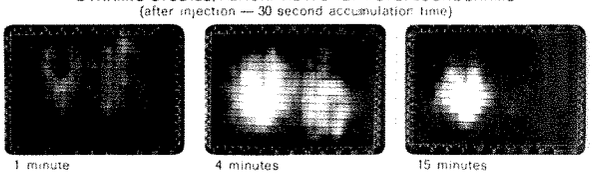
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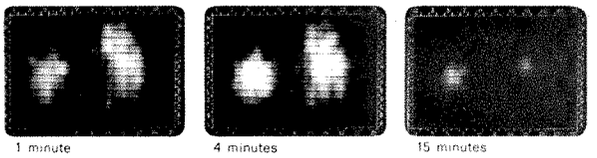
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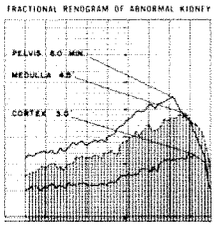
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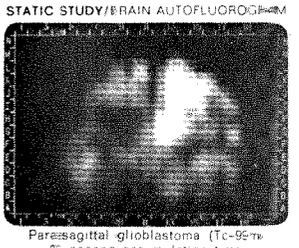


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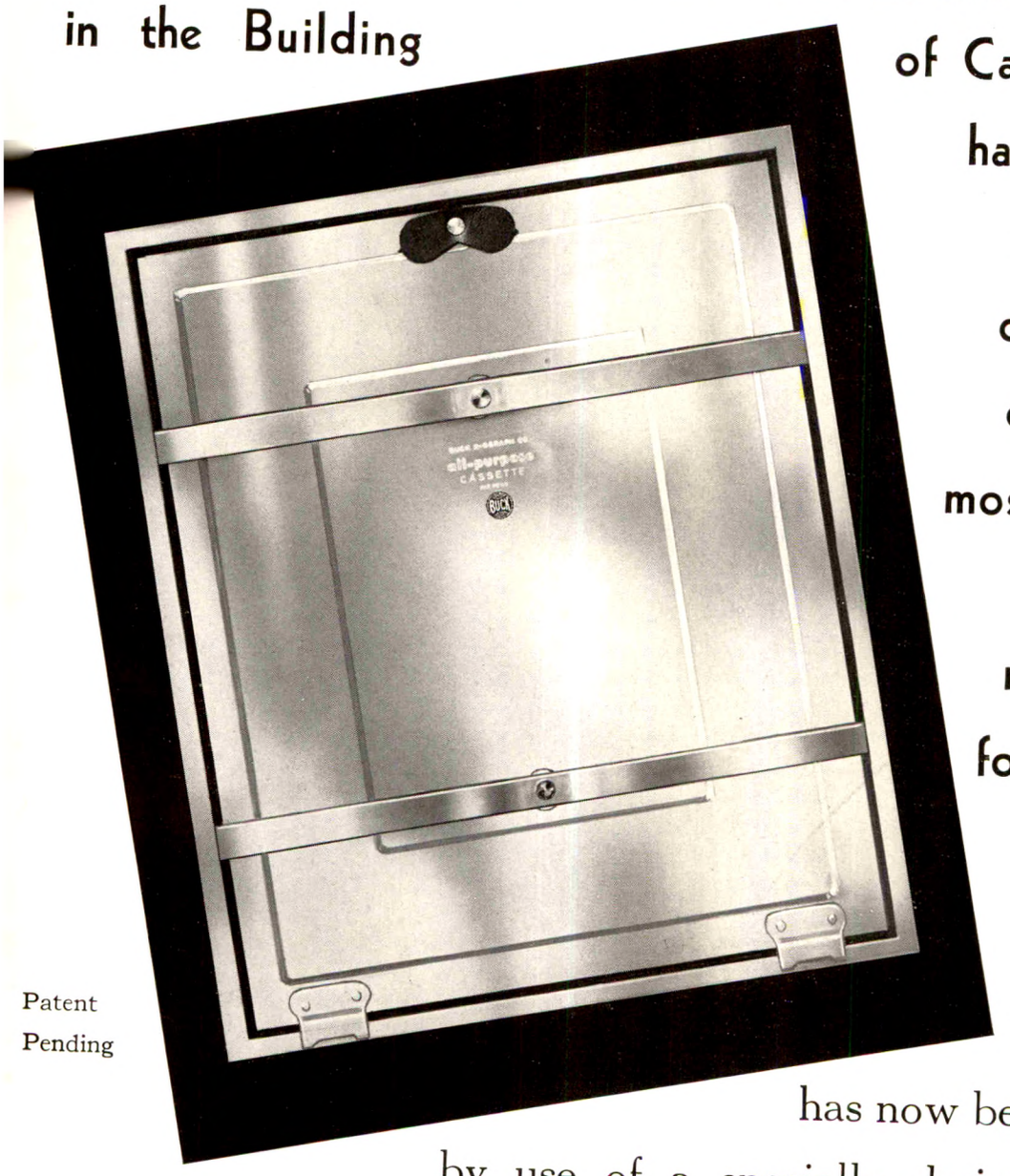
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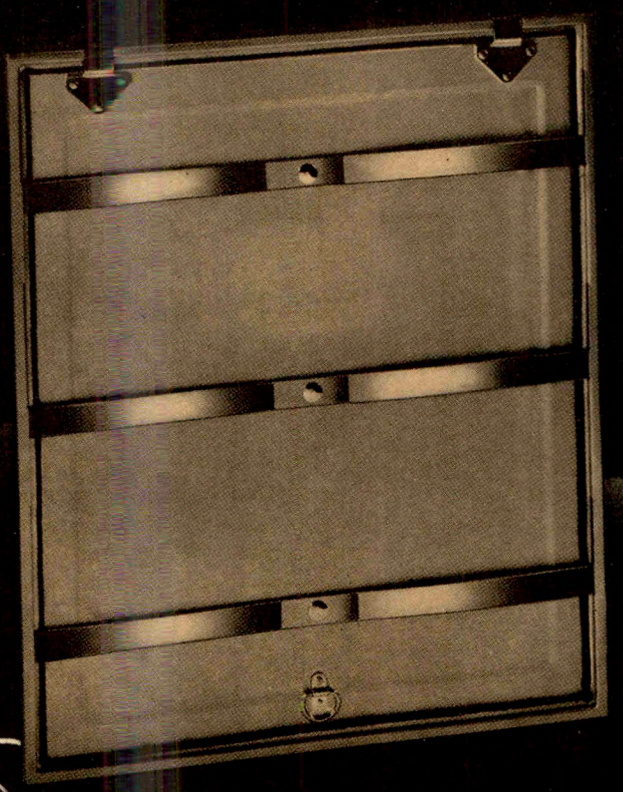
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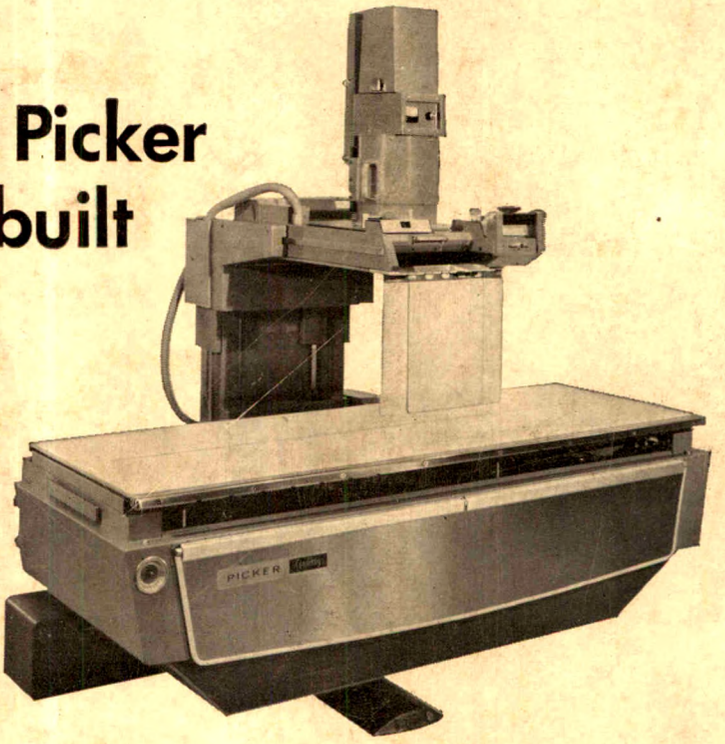
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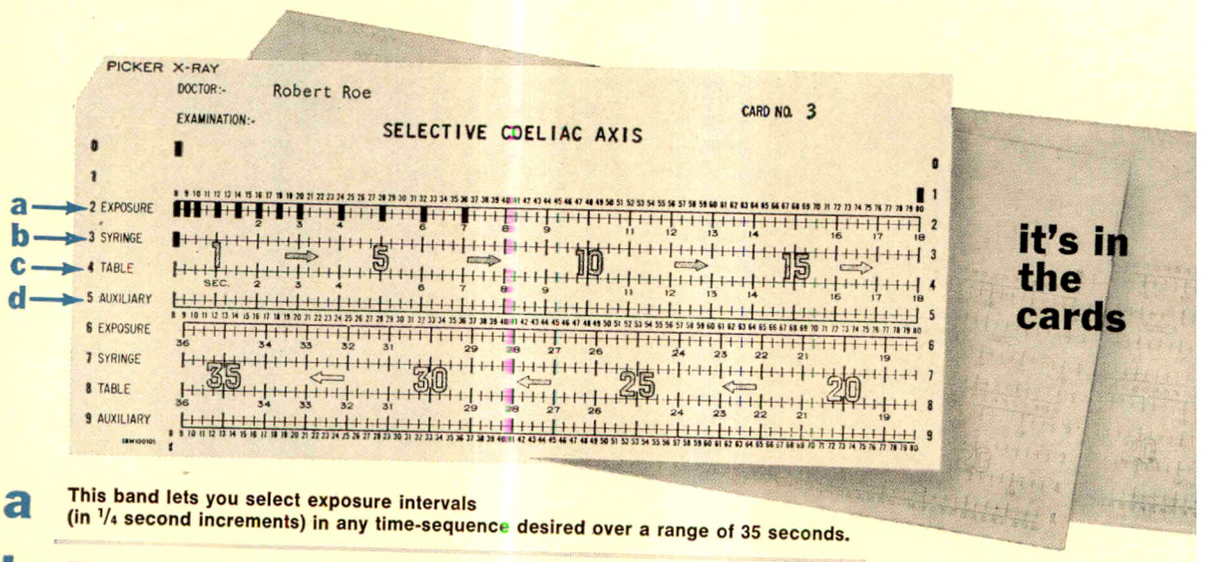
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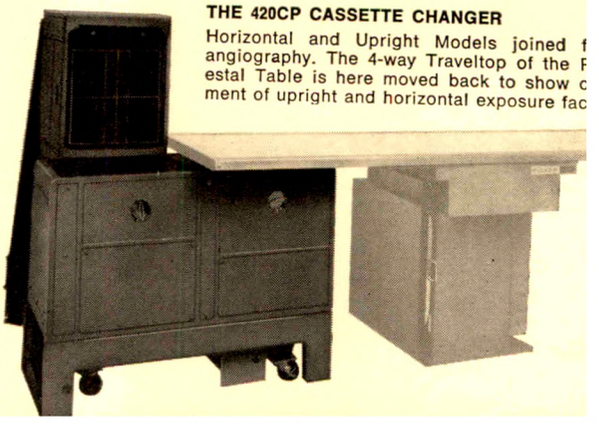
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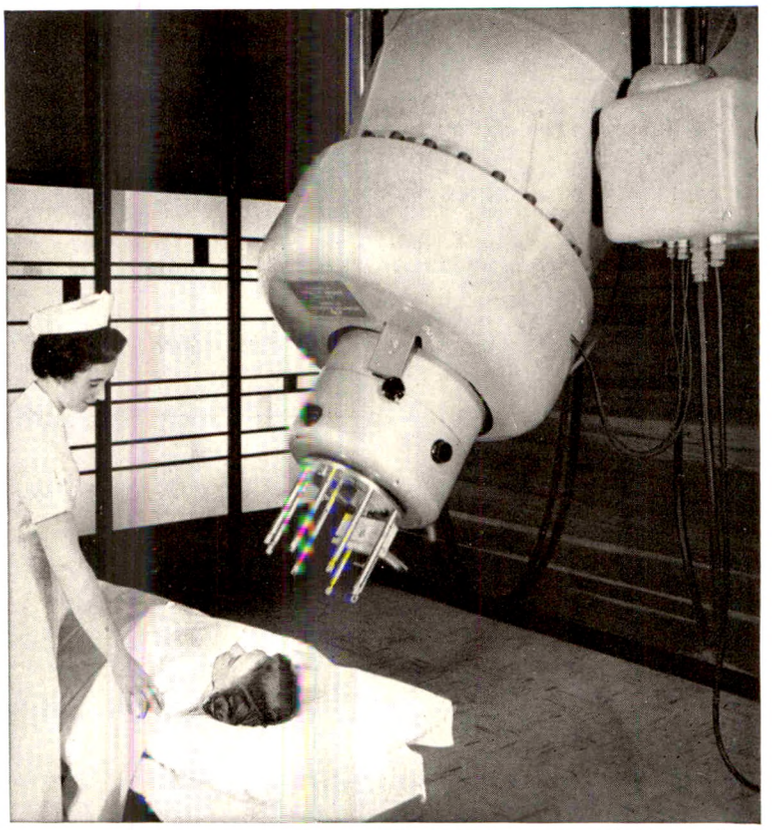
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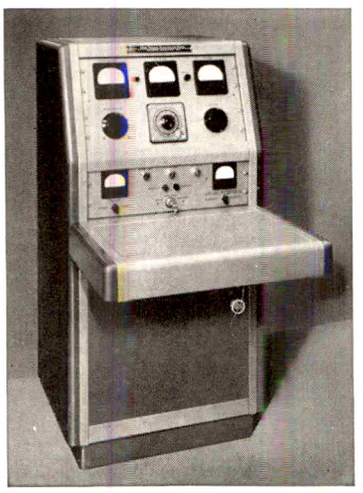


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"...[pulmonary embolism] may exist in a grave form for a considerable time without objective signs being present on physical examination or routine chest films."[1]

Pulmonary embolism is a mimic. Because its symptoms resemble those of other cardiorespiratory diseases—particularly myocardial infarction[2,3] and pneumonia[4]—investigators have long sought simple and certain methods of diagnosing it.

Many diagnostic clues—but often no clinical picture

Until a few years ago diagnosis depended primarily on the clinical history, physical findings, chest films, electrocardiograms, angiography, and pulmonary function studies. Each of these was helpful. Sometimes not even *all* of them were conclusive.

Surgery, prolonged immobilization, metastatic carcinoma and trauma often precede pulmonary embolism—but are not necessarily followed by it. Pain, dyspnea, hemoptysis may signal pulmonary embolism—but they aren't necessarily peculiar to it. The electrocardiogram may be normal in spite of it.[5] And there is no pathognomonic radiographic picture of pulmonary embolism.[5]

To be clinically valuable, however, a new diagnostic test should meet two criteria:
1. it should be correlated with known pathology; i.e., it should be carefully compared with other diagnostic procedures;
2. it should offer information not attainable as easily or as safely by accepted tests.[6]

Pulmonary arteriography meets the first criterion and is a most reliable diagnostic tool. It is, however, a time-consuming procedure and one that requires experienced personnel.[2]

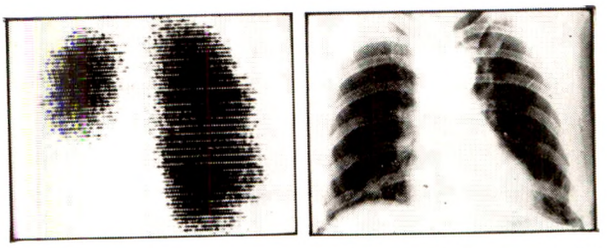
"...lung scintiscanning can detect an obstruction of the pulmonary circulation as soon as it is established."[7]

Not only is the diagnostic procedure of lung scanning both safe and easy,[2] but there is information that is not attainable on chest films. "...it appears that the lung scan can point to the site of the embolic lesions before signs of lung infarction are recognizable on plain chest films."[1]

The scan and the x-ray shown confirm this statement.* The photoscan of this female patient, aged 58, was taken August 13, 1965 with Albumotope-LS (Squibb Aggregated Radio-iodinated [I^{131}] Albumin [Human]). Pulmonary emboli are clearly evident. The x-ray, taken the same day, shows no radiographic evidence of pulmonary emboli.

Lung scanning meets both criteria for a clinically valuable diagnostic test. Findings are correlated with pulmonary function studies, angiography, pathology and the clinical state of the patient. And, scanning with Albumotope-LS has been proven to be "simple, rapid, and safe in the diagnosis, localization and ultimate fate of pulmonary emboli."[2] But the lung scan should not be relied upon as the only diagnostic procedure in the diagnosis of pulmonary embolism.[1]

*Illustrations furnished through the courtesy of George V. Taplin, M.D., Harbor General Hospital, Torrance, California.



Dosage and Scanning Procedures: Recommended scan doses of 150 to 300 microcuries of Albumotope-LS (Squibb Aggregated Radio-iodinated [I^{131}] Albumin [Human]) depending on the instrumentation available and the technics employed. Scanning can immediately follow administration of slow intravenous injection or be delayed up to 1 to 1½ hours depending on preferred technic.

Side Effects and Precautions: Extensive clinical use of Albumotope-LS has not borne out the hypothetical possibility that particles of large size might induce deleterious cardiovascular or cerebrovascular effects. No antigenic properties have been specifically related to this product; one patient with a known history of angioneurotic edema, who had been given Lugol's solution in conjunction with aggregated radioalbumin similar to Albumotope-LS, developed urticaria.

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References: 1. Haynie, T. P., et al.: J. Nucl. Med. *6*:613, 1965. 2. Sabiston, D.C., Jr., and Wagner, H.N.: Ann. Surg. *160*:575, 1964. 3. Cooley, R.N., and Donner, M.W.: Am. J. M. Sc. *247*:601, 1964. 4. Wagner, H.N., et al.: New England J. Med. *271*:377, 1964. 5. Hinshaw, H.C., and Garland, L.H.: Diseases of the Chest, ed. 2, Philadelphia, W. B. Saunders Co., 1963, pp. 438-9. 6. Dworkin, H.J., et al.: Michigan Med. *64*:829, 1965. 7. Quinn, J.L., et al.: Radiology *82*:315, 1964. 8. Taplin, G.V., et al.: Health Physics *10*:1219, 1964.

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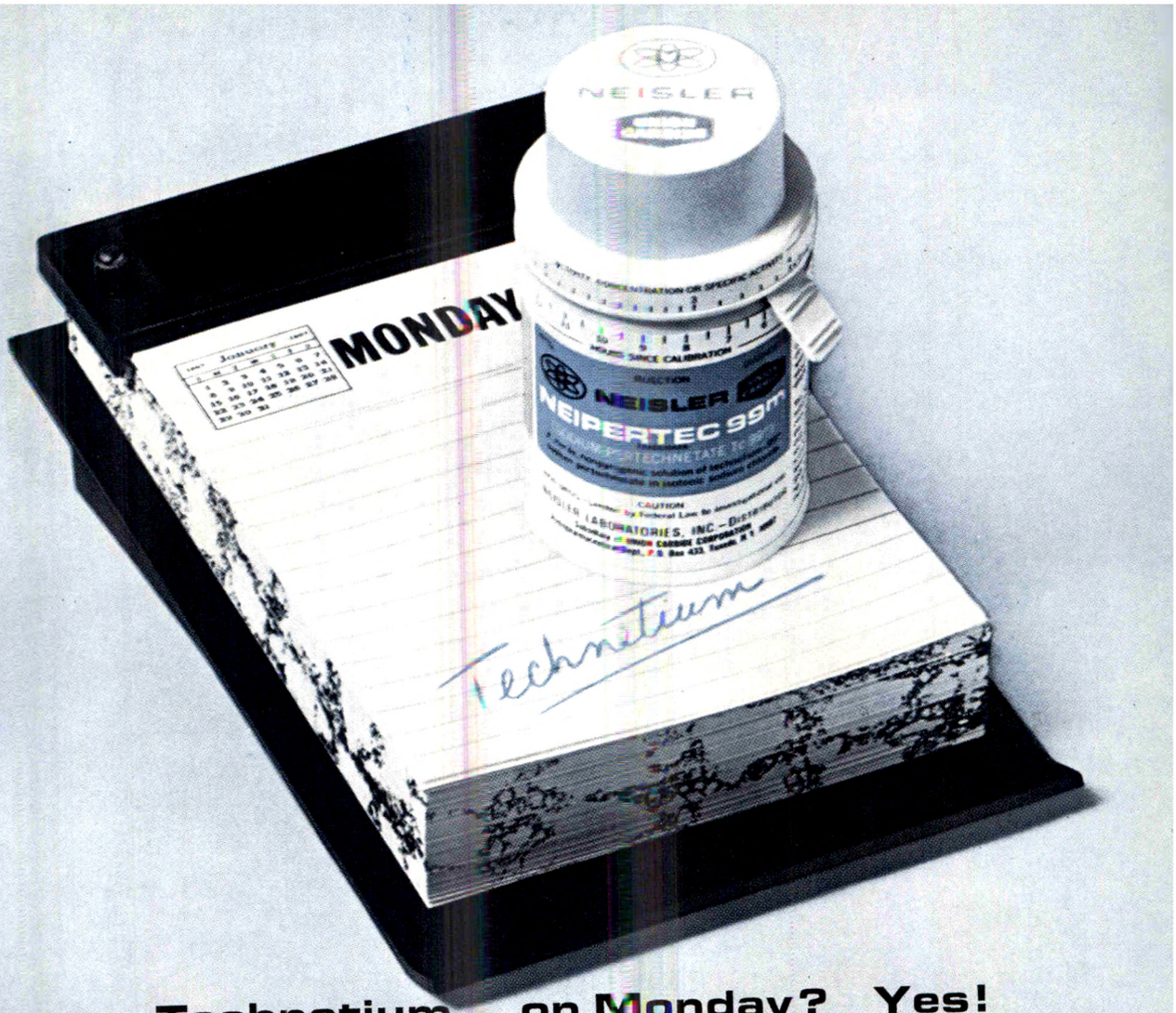
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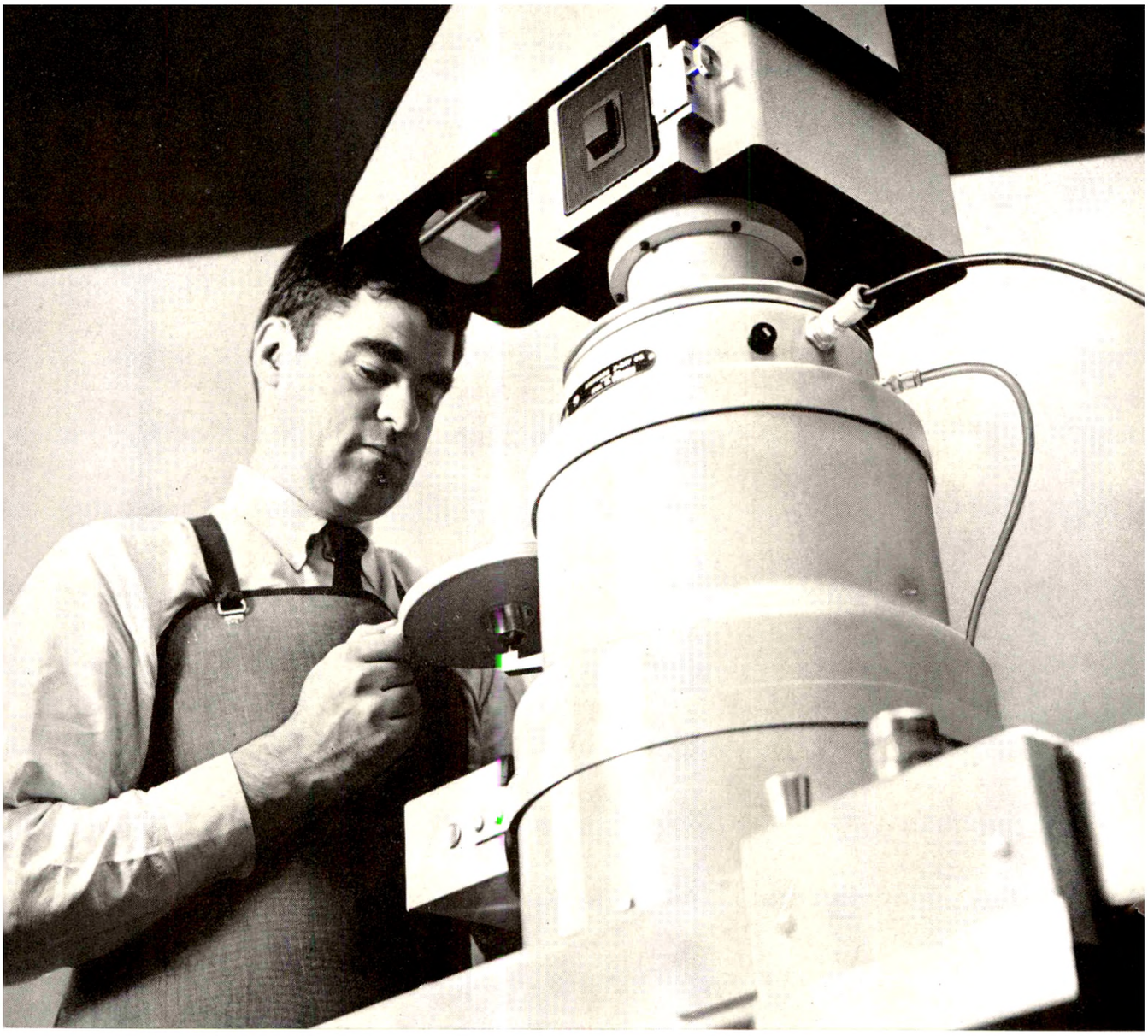
1. J. G. McAfee, C. F. Fueger, H. S. Stern, H. N. Wagner, Jr. and T. Migita: Tc^{99m} pertechnetate for brain scanning, *J. Nucl. Med.*, 5:811, 1964.

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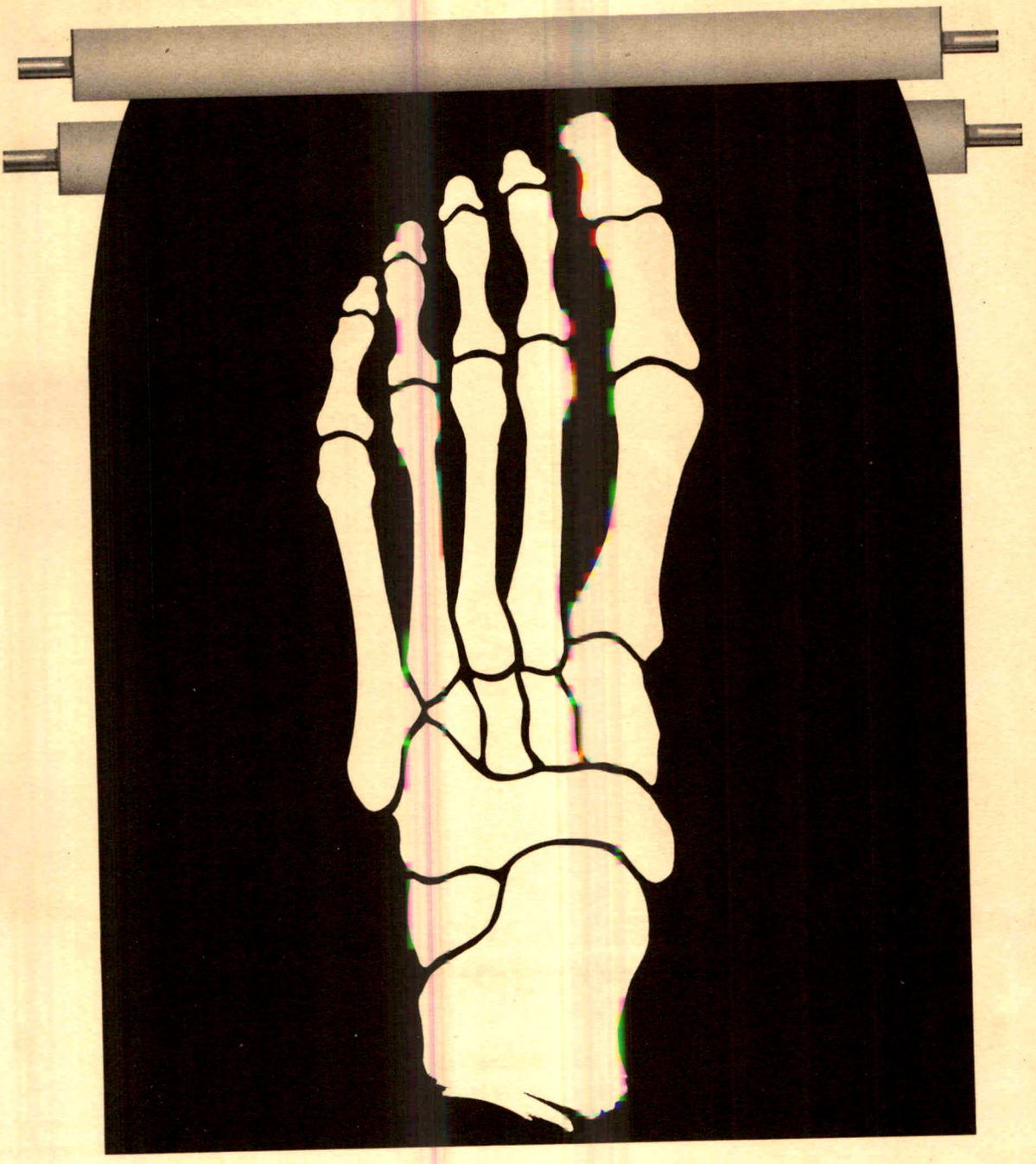
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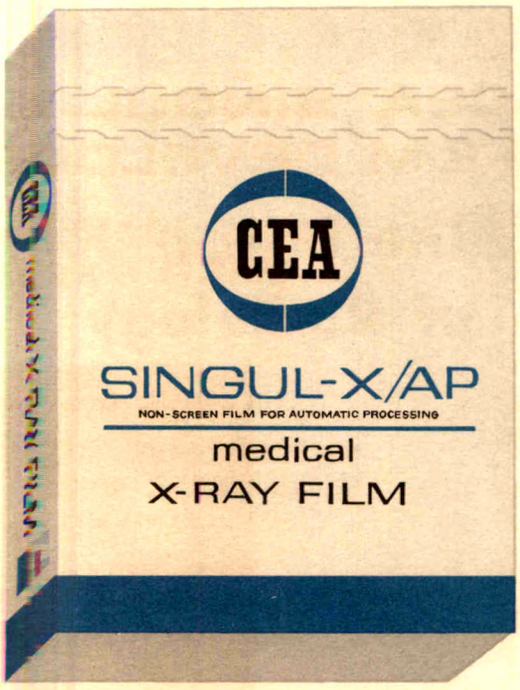
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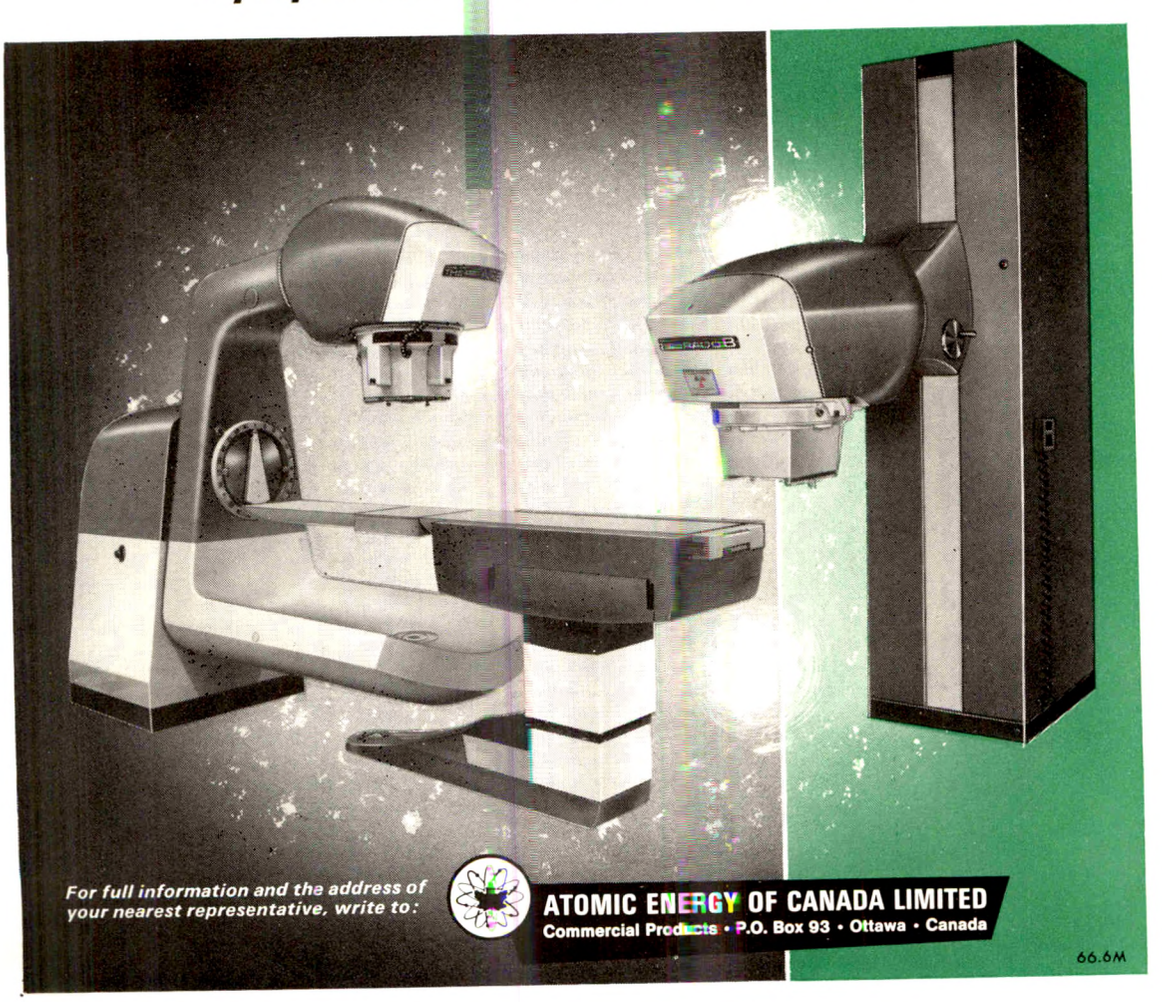
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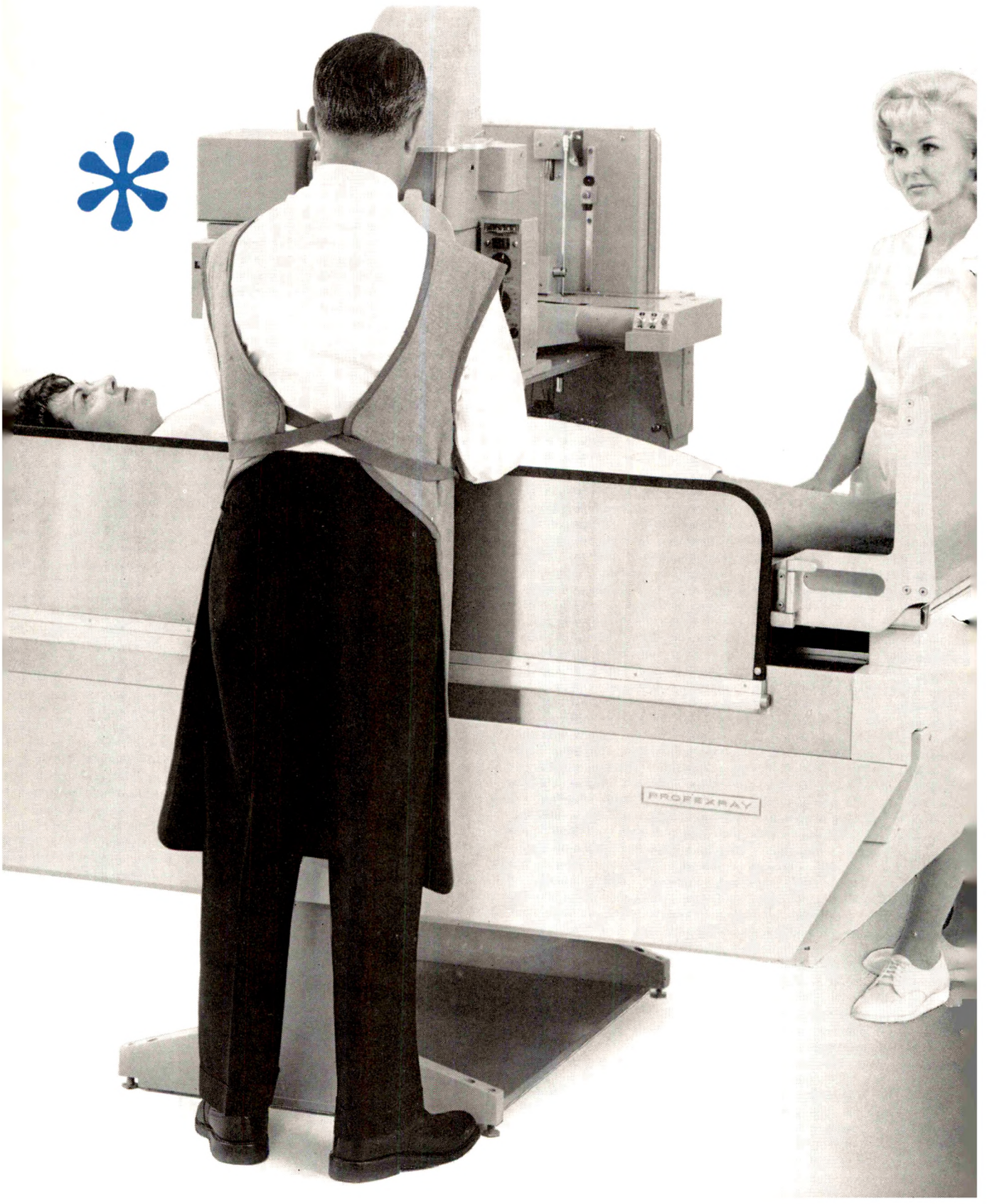
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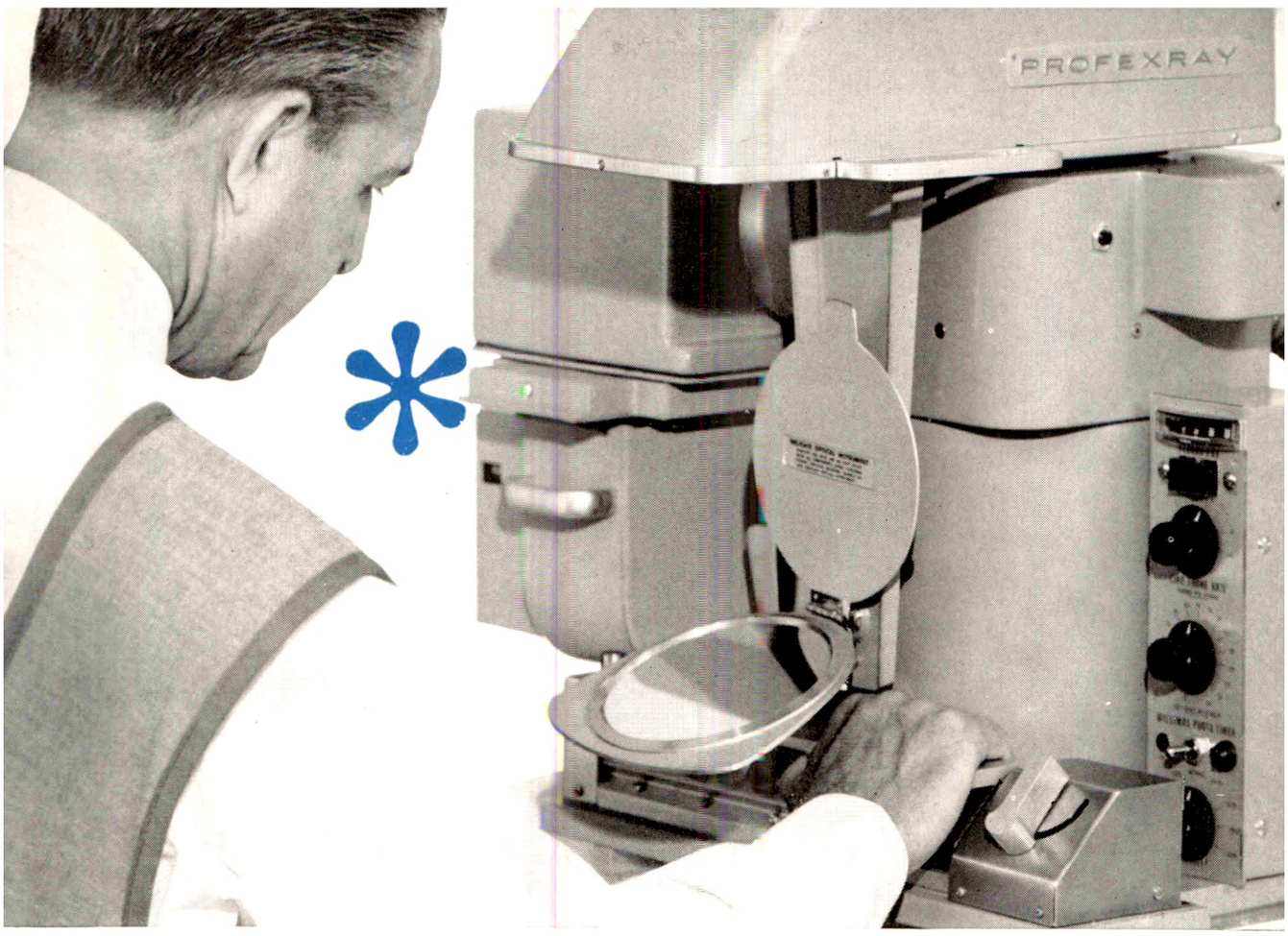


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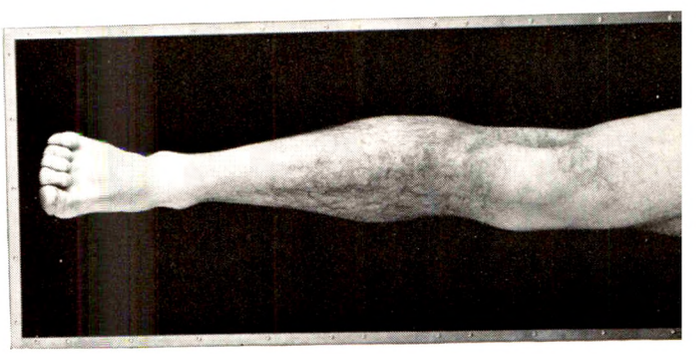
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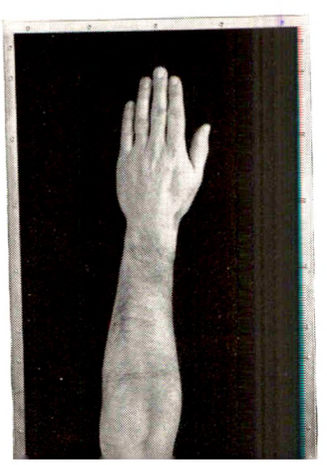
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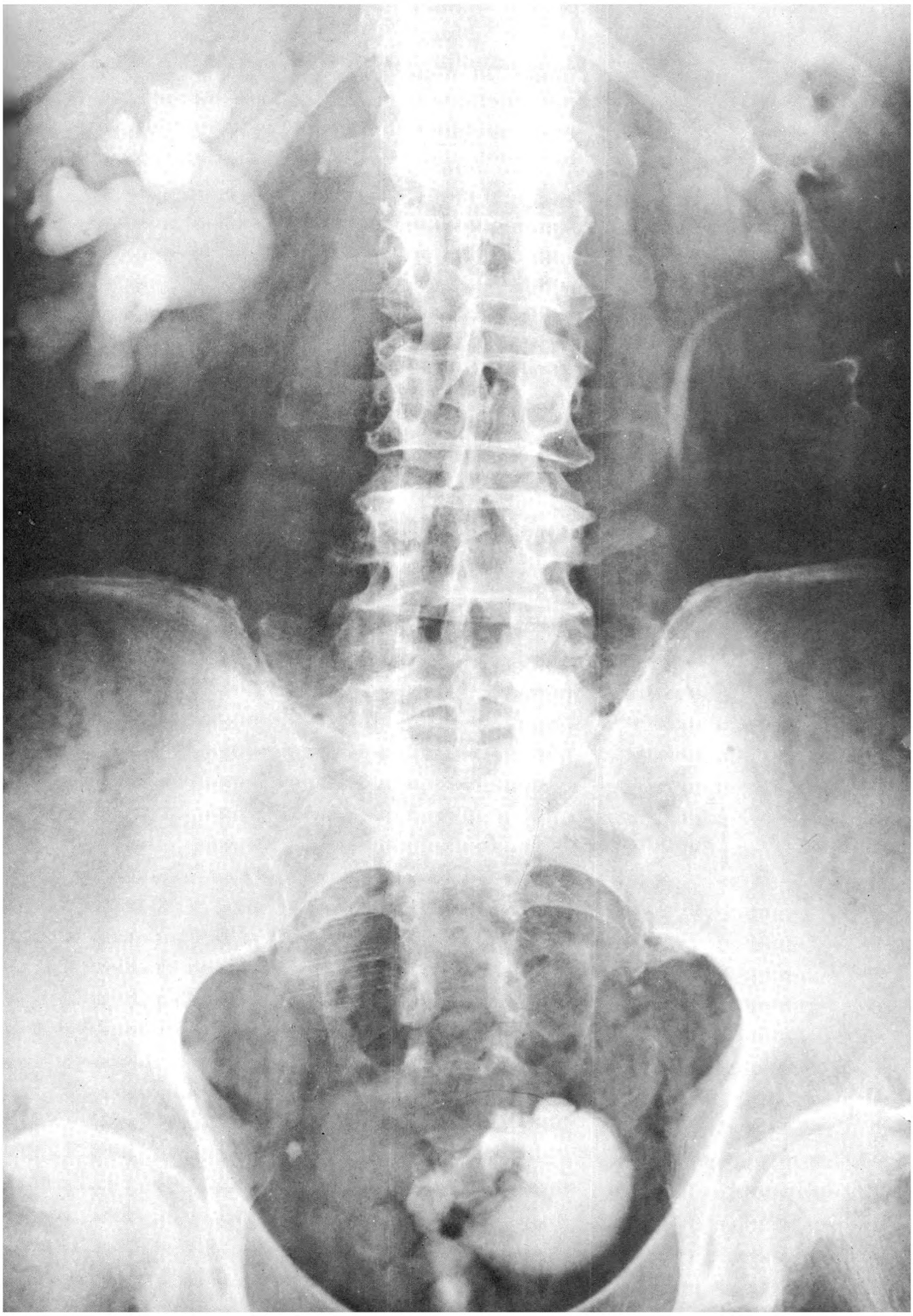




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Side effects: Severe, life-threatening reactions are rare; when they occur, they suggest hypersensitivity to the contrast agent. Transient flushing and nausea during injection may occur. In rare instances, anaphylactoid reactions may occur.

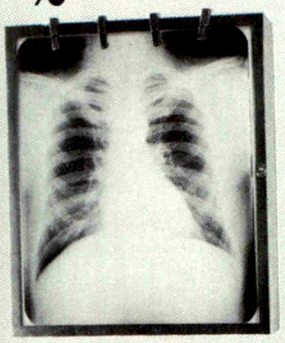
Precautions: I.V. test dose may be given. Use with caution in the event of an untoward reaction to the test dose and in extreme age, severely debilitated patients, cyanotic infants, patients with chronic pulmonary emphysema, advanced arteriosclerosis, severe hypertension, cardiac decompensation, and recent cerebral embolism or thrombosis. The possibility of thrombosis should be borne in mind when percutaneous techniques are employed. For full information, see Product Brief.

*Margulis, A. R., and Heinbecker, P.: Am. J. Roentgenol. *86*:103 (July) 1961.

SQUIBB

Squibb Quality—the Priceless Ingredient

Rx for good radiographs



The right film.

The right screen.

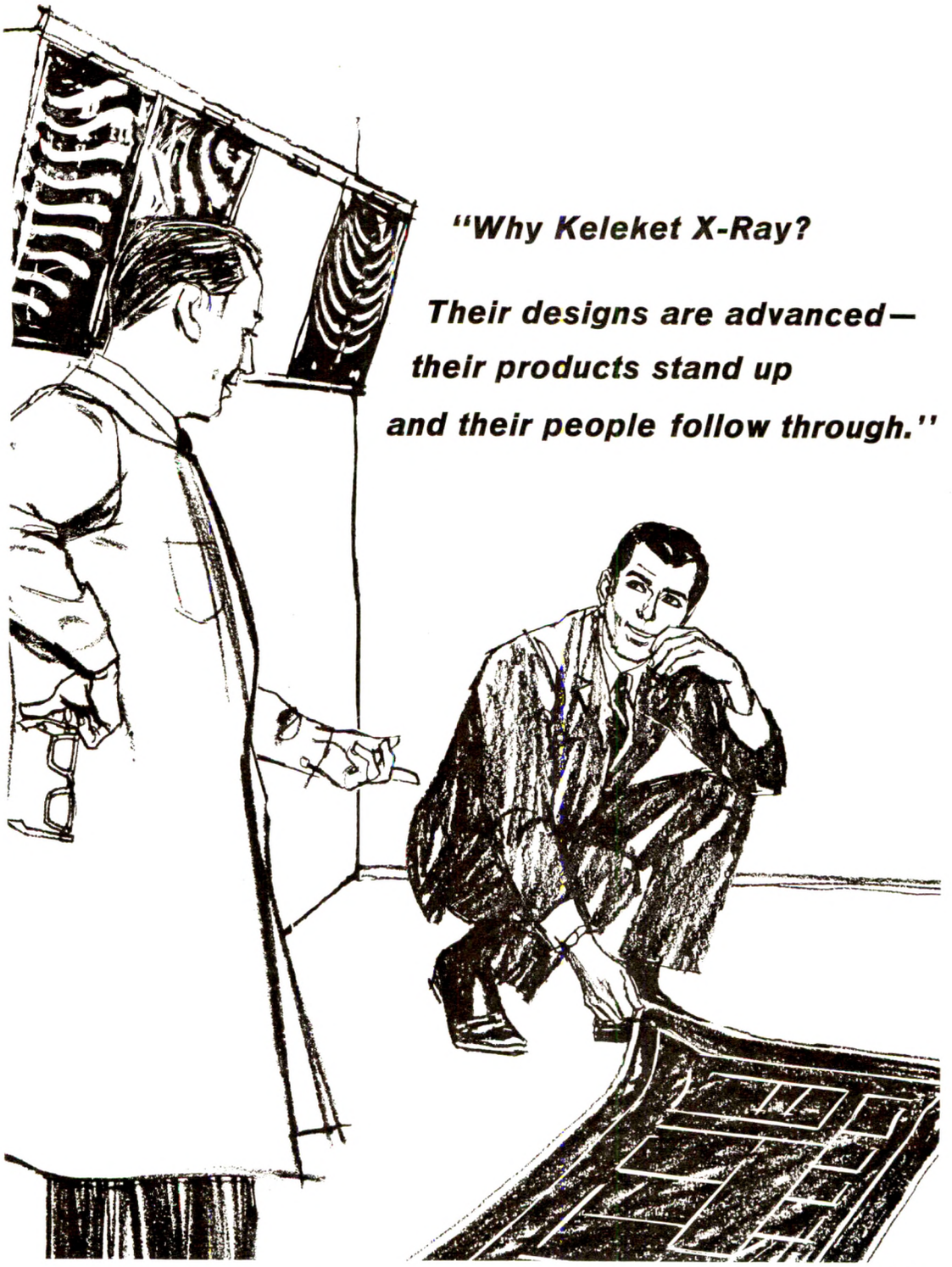
The right film for most radiographic investigations is one which offers high contrast, medium speed, fine grain and very low fog level. Ilford Standard is that film—at a cost appreciably lower than for other films of comparable quality. *Standard is compatible with the new "half-cycle" or "double-capacity" automatic processing techniques.*

The right screen must be fast, with outstanding definition—and Ilford Fast Tungstate Intensifying Screens are the ultimate in the field; their definition is equal to that of most screens with half the speed. Put these two fine products in the hands of a skilled technician and you will have gone a long way toward improving your radiographs.

ILFORD INC.
37 West 65th Street
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"Why Keleket X-Ray?

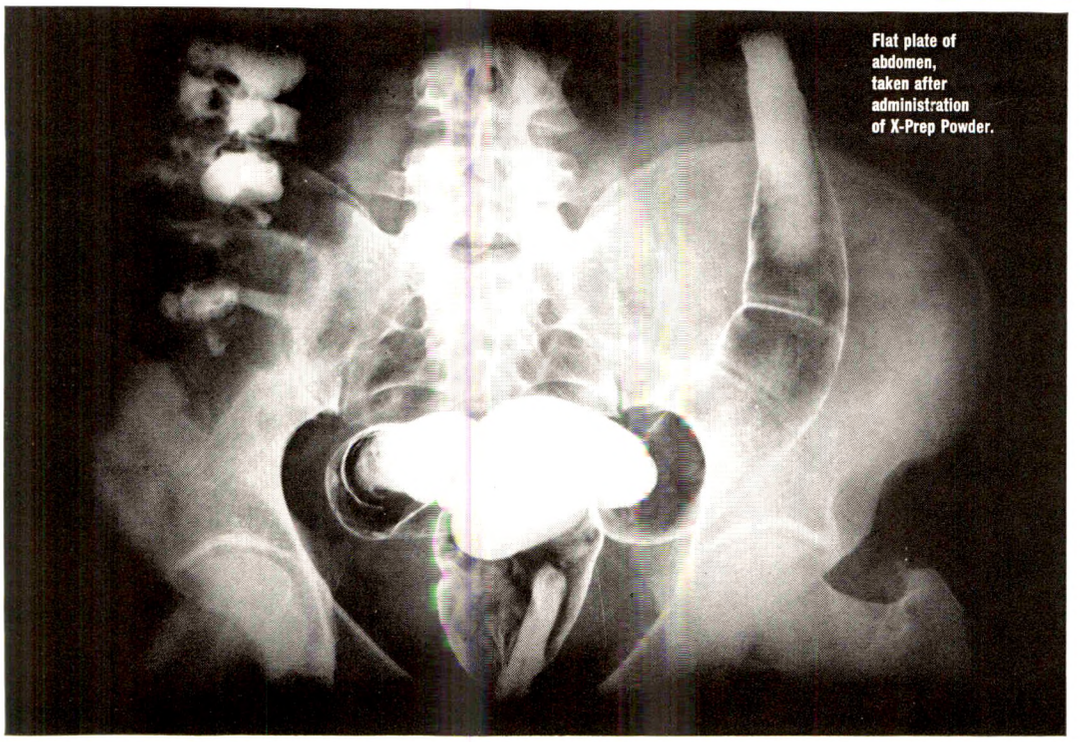
Their designs are advanced—
their products stand up
and their people follow through."

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NOW...
A ONE-STEP PROCEDURE FOR EFFICIENT CLEANSING OF THE COLON PRIOR TO RADIOGRAPHY



Flat plate of abdomen, taken after administration of X-Prep Powder.

Superior Visualization...Fewer Retakes with

X-PREP
POWDER
(standardized senna concentrate)
Easy-To-Mix With Water
¾ oz. can
(complete adult dose)

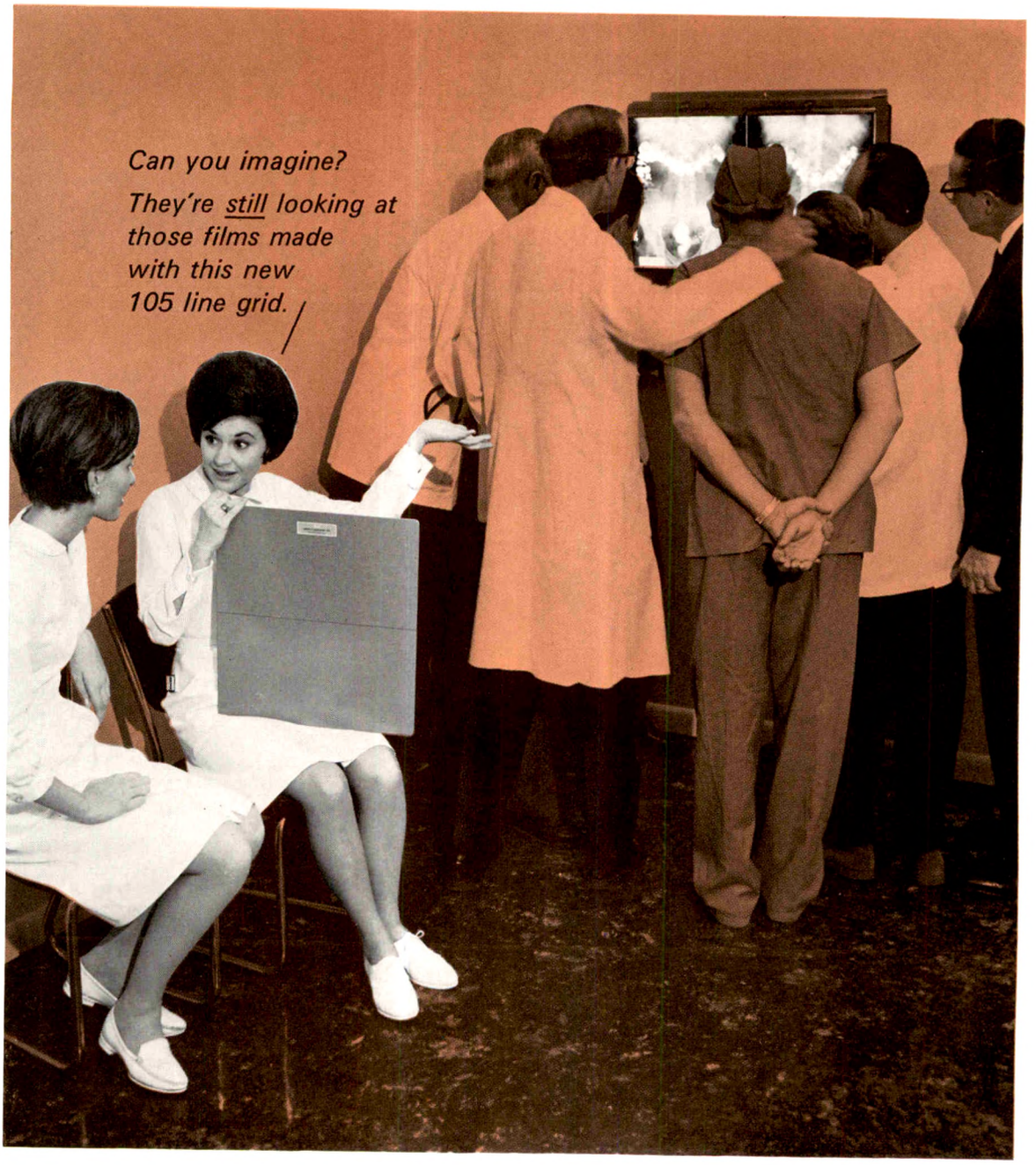
X-PREP
LIQUID
(standardized extract of senna fruit)
Ready-To-Drink
2½ oz. bottle
(complete adult dose)

SIMPLE, PALATABLE, SINGLE-DOSE PROCEDURE FOR GOOD BOWEL PREPARATION

A reliable, predictably effective bowel evacuant that achieves efficient cleansing of the colon by virtually colon-specific peristaltic stimulation. Reduces or eliminates the need for preparatory enemas. Highly palatable and easy-to-take, X-PREP Powder/Liquid encourages better patient cooperation. All the patient has to do is drink the preparation between 2 and 4 P.M. on the day prior to radiography.

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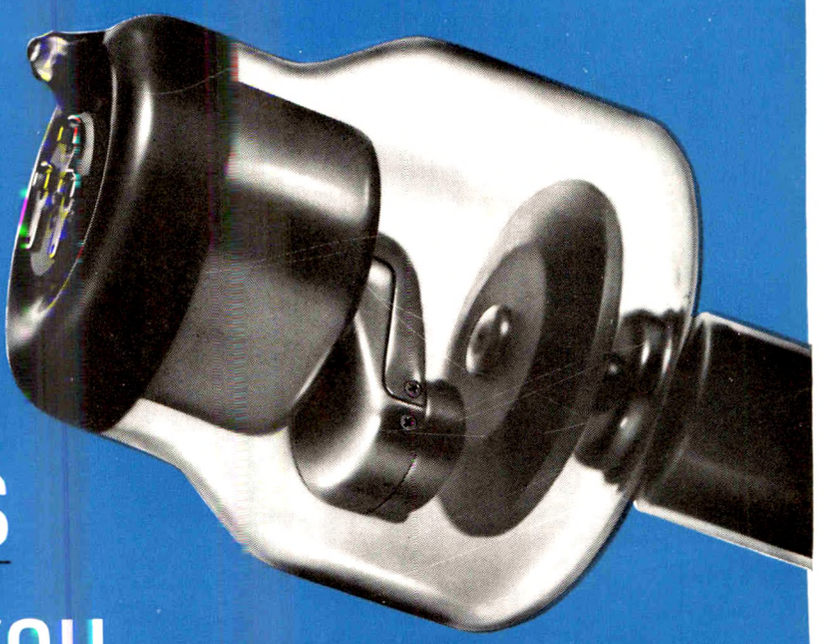
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- improved quality for greater diagnostic clarity

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1. They provide insurance against any gas evolution that may occur during an accidental overload or extremely heavy duty service. The Dunlee getter is not and has never been intended to be used as a pumping device to speed up our exhaust processes.
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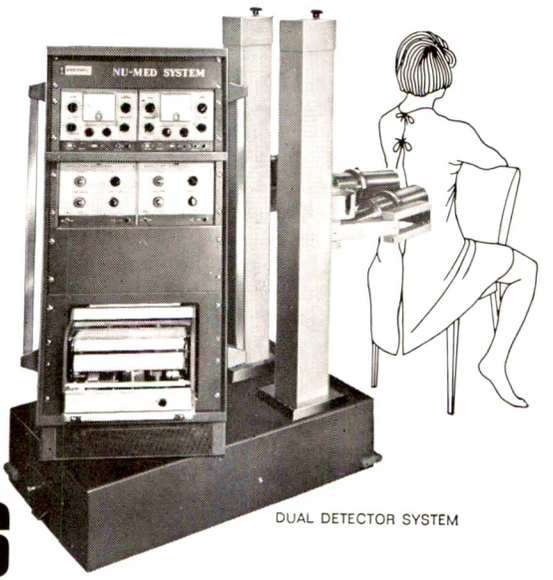
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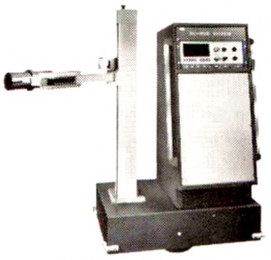
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FOR CLINICAL DIAGNOSIS OF OPERATING CONDITIONS OF THE RENAL SYSTEM!!



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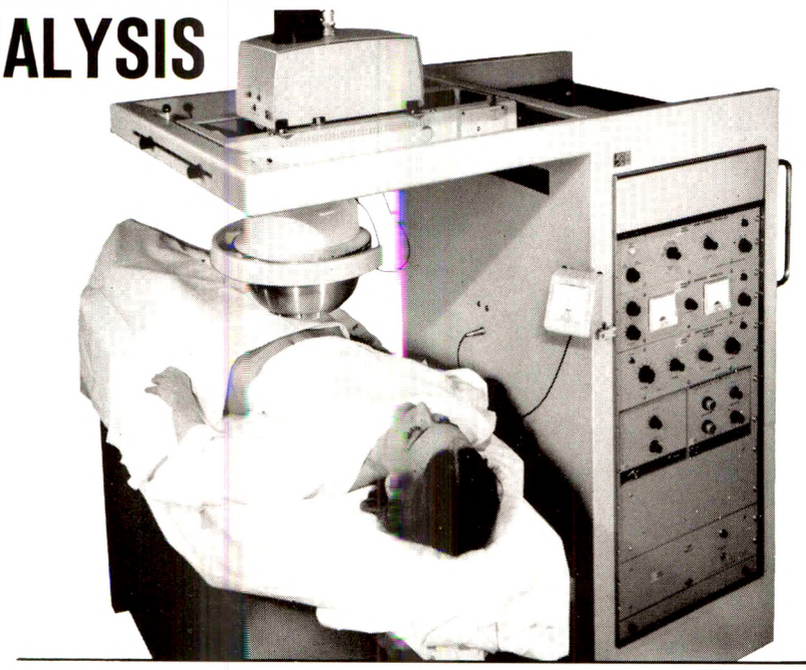
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MODEL CS-500A-3
3-inch probe

MODEL CS-500A-5
5-inch probe

In nuclear medicine, the CS-500 Medical Scanner is a valuable clinical tool for organ or tumor visualization, providing a powerful adjunct to the diagnostic skills of the physician.

The CS-500 features photorecording on X-ray film and teledeltos paper recording to display the distribution and concentration of isotopic labeled compounds localized in selected organs and areas of the human body. Studies utilizing the most recent scanning techniques with newly developed radioactive compounds may be done accurately and quickly.

Truly significant differences are revealed, even at low count rates, by the electronic elimination of background, and expansion of the remaining data photographically over the entire contrast curve.

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Write to the Nuclear Instrument Department for brochure CS-500.

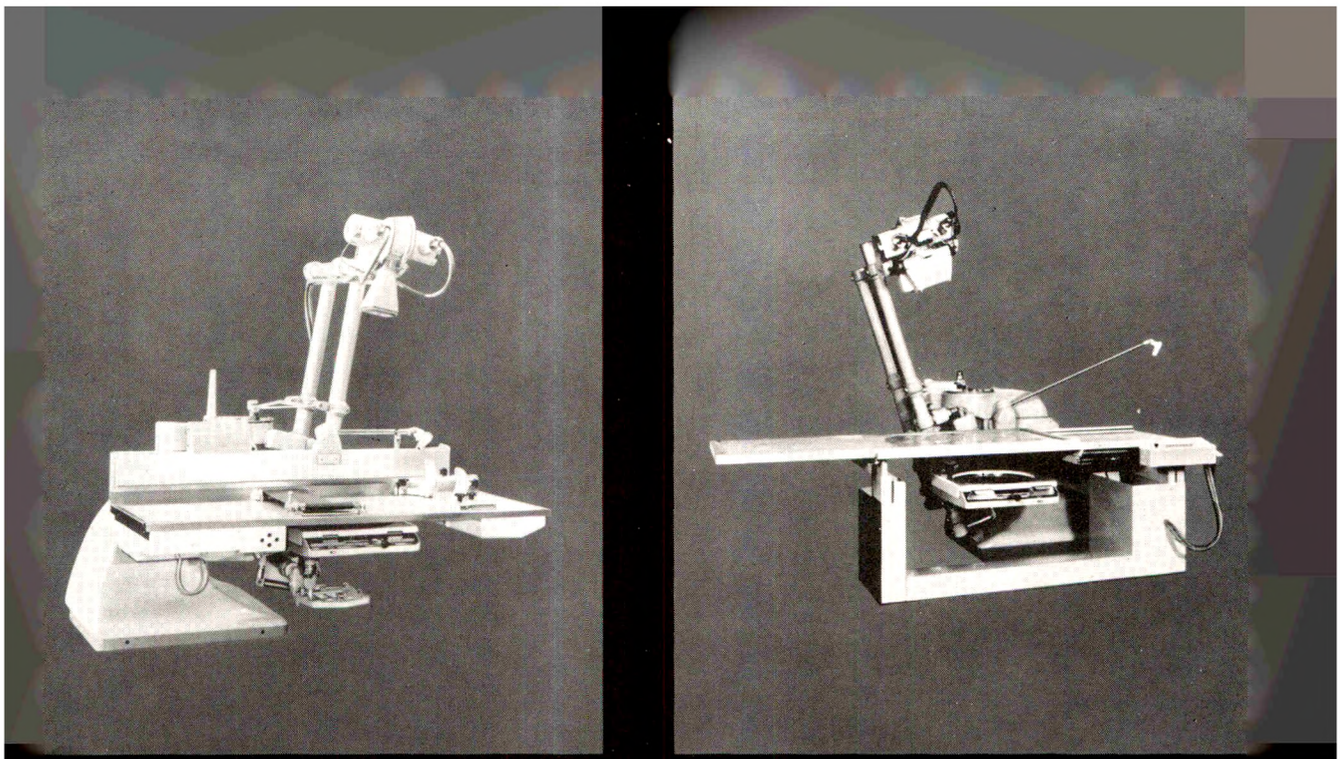
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Both these Norelco tomographic units do anything any other unit will do...

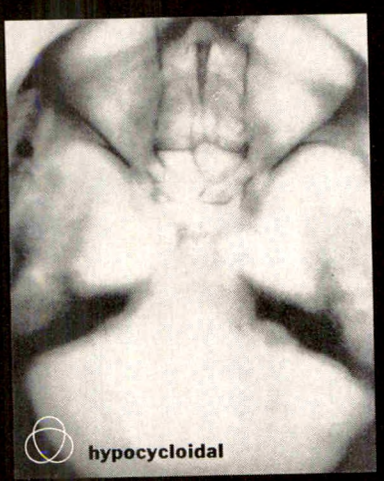


The clearest tomograms of thinnest possible layers are provided by the trajectory and exceptional length (451cm) of the Norelco Polytomes' hypocycloidal movements.

Of course, linear, elliptical and circular movements, with wide choice of swing angle and orientation, are provided for examinations where conventional movements are preferred. Zonography (small angle circular tomography), producing cut of several cm thickness, is also possible a any angle from 0° to 20°.

Focus, tomographic layer and film remai at fixed mutual distances, thereby preservin constant enlargement factors of 1.3, wit secondary holder for magnification of 1.6 Removable Grid: 10:1, 110 lines.

but *only* the Norelco units do this



MANUFACTURED FOR NORELCO BY MASSIOT PH

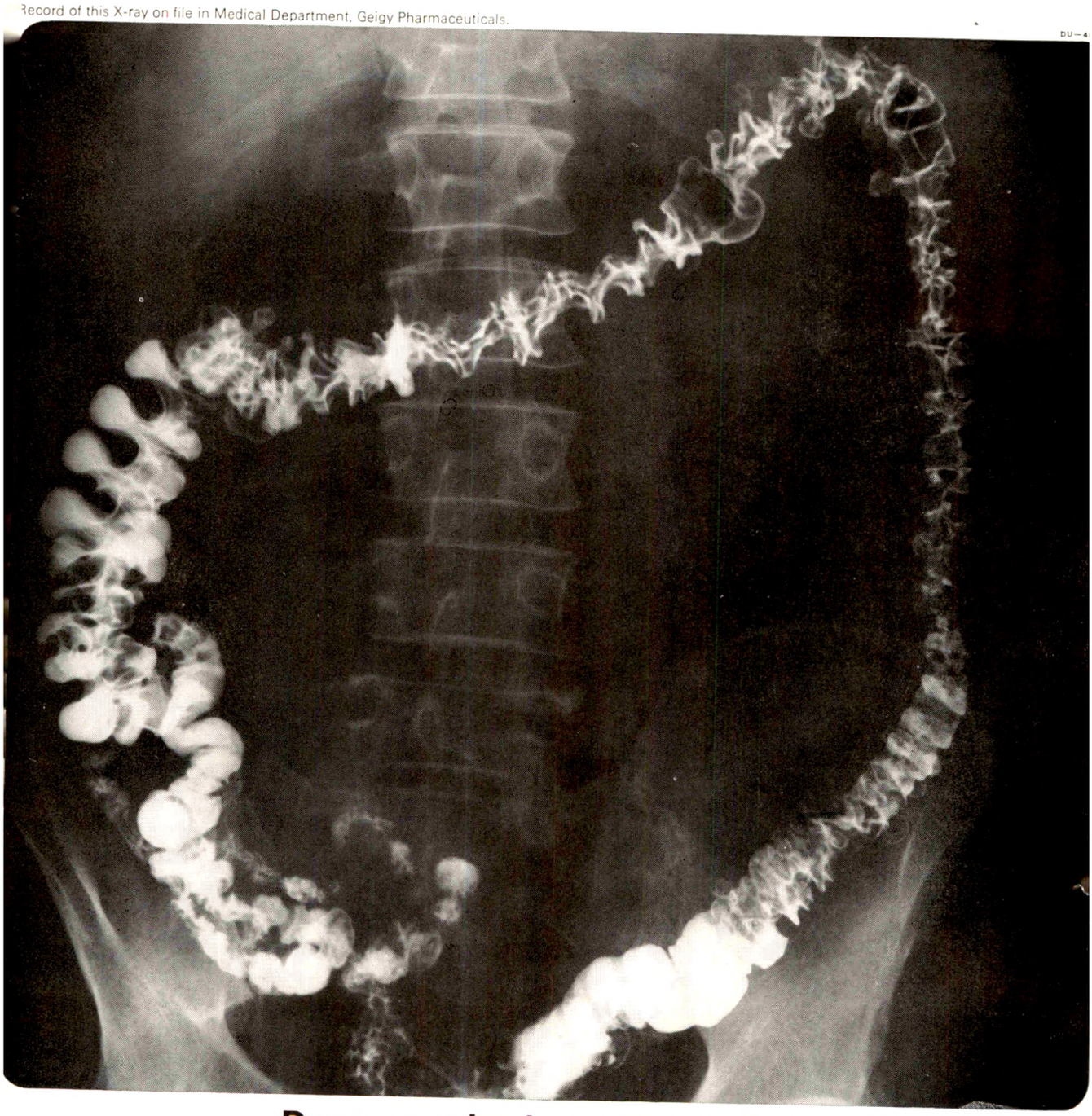
The Universal Polytome (*above, left*) tilts, permitting tomography in any position from horizontal to vertical. Longitudinal tabletop movement is provided. Conventional Bucky exposures are possible with the Horizontal Polytome (*above, right*), which is equipped with a floating tabletop providing a generous range of longitudinal and transverse travel. Both models are equipped with a lightbeam positioning device, compression band, headclamps, footrest and stool.

Our systems engineers will be pleased to give you detailed information. Write or call North American Philips Company, Inc., Professional Products Division, Medical Department, 100 East 42nd Street, New York, N.Y. 10017. In the Chicago area: 749 Howard Street, Evanston, Illinois.

Norelco

Record of this X-ray on file in Medical Department, Geigy Pharmaceuticals.

DU—4



Does your barium enema prep afford visualization of diverticuli this clearly?

These references from the literature describe what results Dulcolax provides.

In both the pre-evacuation and post-evacuation films of 200 patients given barium enemas, "...Dulcolax tablets and Dulcolax suppositories gave a considerably higher number of excellent and good results..." than did castor oil and cleansing enemas, Dulcolax tablets and cleansing enemas, or castor oil and a Dulcolax suppository.
Mouton, R.A., and Nice, C.M., Jr.: J. Louisiana M. Soc. 117:158, 1965.

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In preparation for barium enema, Dulcolax produced a satisfactory bowel evacuation in 96% of 500 cases. Need for repeat examinations was greatly reduced in comparison to castor oil preparation.
Raymond, O., et al.: Canad. M.A.J. 82:1077, 1960.

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GENERAL ELECTRIC



TELETROL II

DIAGNOSTIC X-RAY SYSTEM

Everything Remote But the Benefits

- Remote Patient Positioning
- Remote Television Viewing
- Remote Bucky/Spot-Filming
- Remote 16-MM Cine-Filming
- Remote 70-MM Spot-Filming
- Remote Compression Control

Here's the diagnostic x-ray system that speeds patient handling, eliminates cumbersome lead clothing, while maintaining close patient/radiologist communication.

TELETROL II

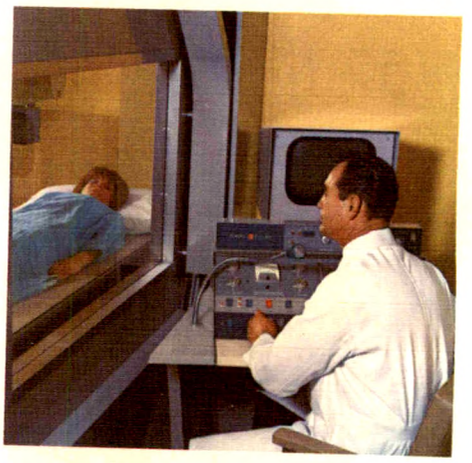
DIAGNOSTIC X-RAY SYSTEM

for High Volume Work Loads

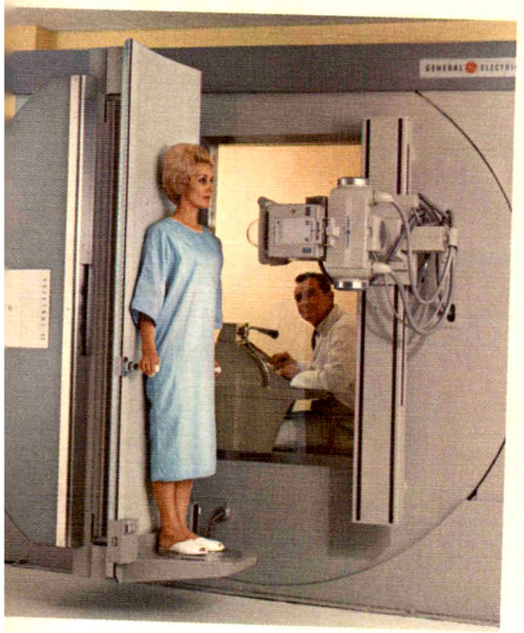
Speeds Up Procedures as much as 50%—New diagnostic technics and rapidly increasing patient loads place heavy demands on radiology departments. Unique integration of table, generator and image presentation components into one compact system allows for easy accommodation into most existing rooms without major alteration. One radiologist can perform a variety of procedures—brightly intensified fluoroscopy, 16-mm cine-filming, 70-mm spot-filming and Bucky radiography—*without ever moving from the convenient, radiation shielded control console.* Patients move through rapidly with consistently efficient results. The generator provides 150 kVp for all radiographic technics with independent fluoroscopic kVp.

The Teletrol II is provided with high performance operational features. New transverse table top movement is independent of Bucky. The radiographic tube is automatically aligned for precision recording because it's coupled to the intensifier. A new 4-on-1 serial cassette tray speeds up filming; also accepts conventional standard cassette tray. Rotating foot rest, shoulder rest, grasp handles and safety harness are furnished as standard features.

New Relicon Television System—Teletrol II is equipped with a new high resolution separate mesh vidicon TV camera, available in 525 or 875 line scan rate, featuring 15 megacycle band width and contrast-improving circuitry. Relicon camera and read-out system are designed specifically for image intensification. The monitor has a full 14-inch screen.



Instant Command Control Console—The ultimate in convenience and equipment response is provided by the Teletrol II control console. Operator maintains close patient contact visually through 30¾-inch x 54¾-inch radiation-shielded window and audibly through intercom system.



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INJECTABLE SODIUM PERTECHNETATE ^{99m}Tc

from your own

COMPACT PRODUCTION FACILITIES

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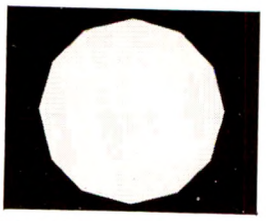
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MACHLETT

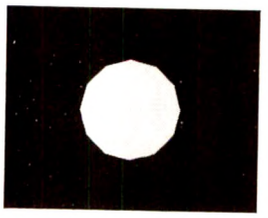
This is Machlett-Videx Round/Rectangular Collimation:

collimaster

Any Geometry Without Attachments



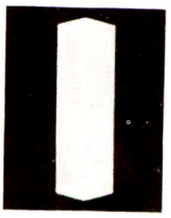
Routine
image areas
(gall bladder)



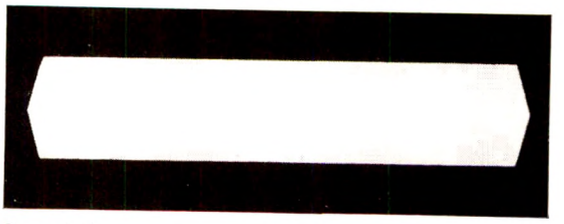
High definition
image areas
(sinus & mastoids)



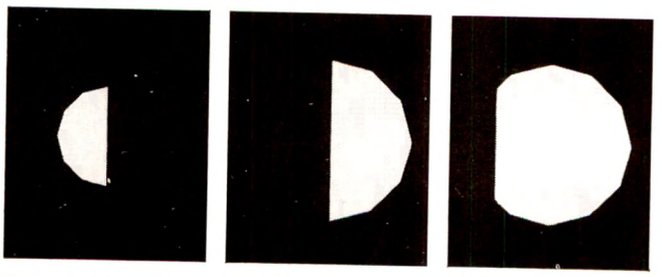
Typical large
area coverage
(abdomen)



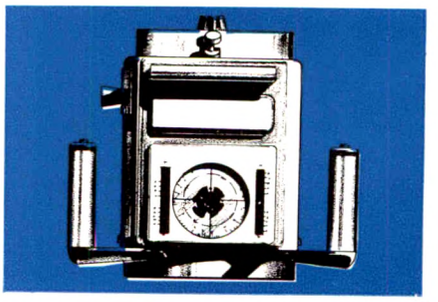
Selective
area coverage
(esophagus)



Special
technique coverage
(femoral arteriogram—14″x36″ at 64″)



Special beam shapes
(mammography)



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THREE-POINT-FIVE film for 3½ minute processing

GEVAERT quality is so inherently good that it has taken just a minor adjustment of our emulsion formula to bring it into line for rapid processing.

THREE-POINT-FIVE film will give you the same, fine diagnostic quality you have learned to expect from GEVAERT.

Your present equipment can be converted within a few hours to accommodate our new THREE-POINT-FIVE.

Contact your nearest GEVAERT representative. He'll be glad to advise you and make all arrangements for the changeover.

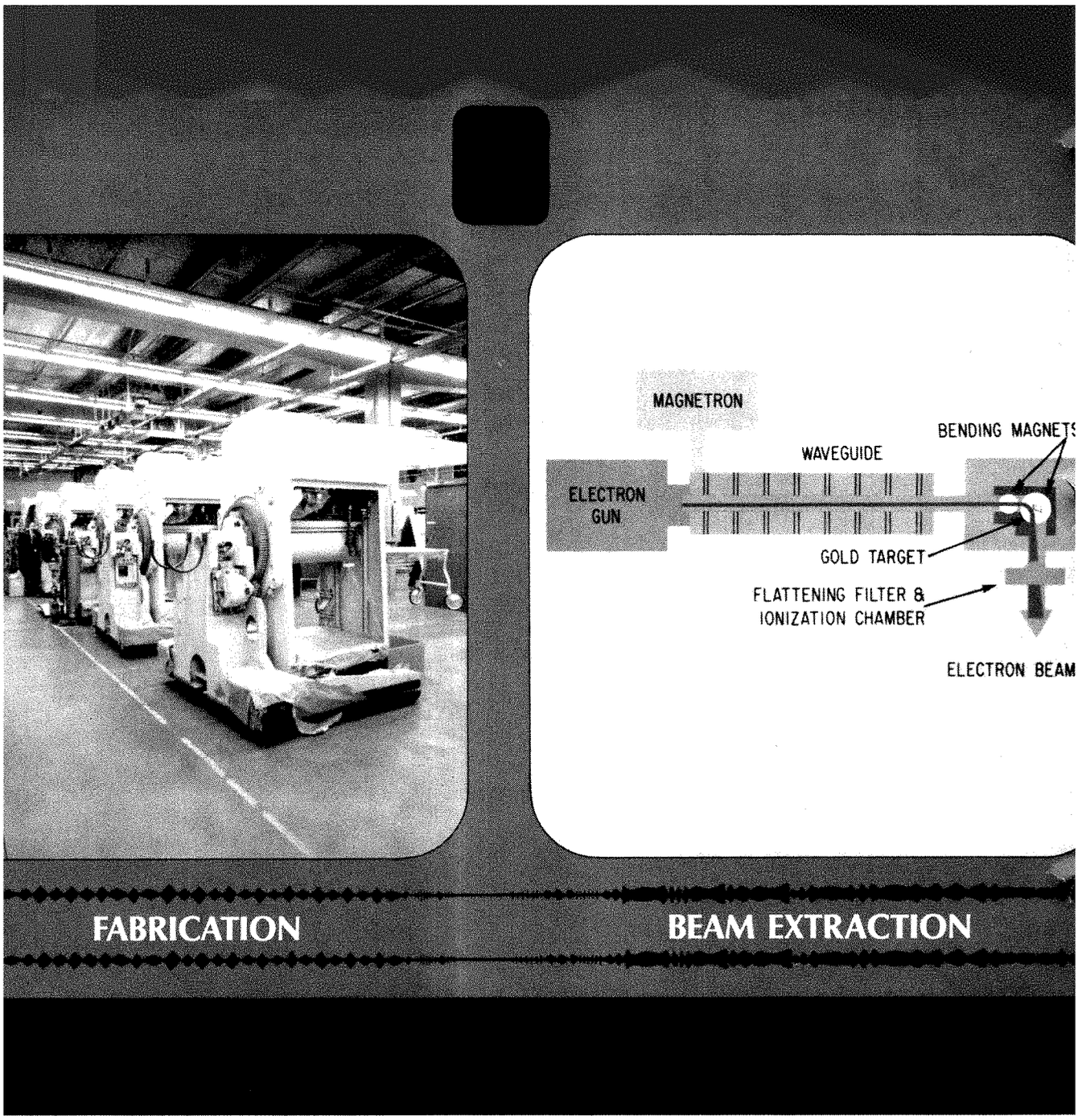
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212 - 255-3700

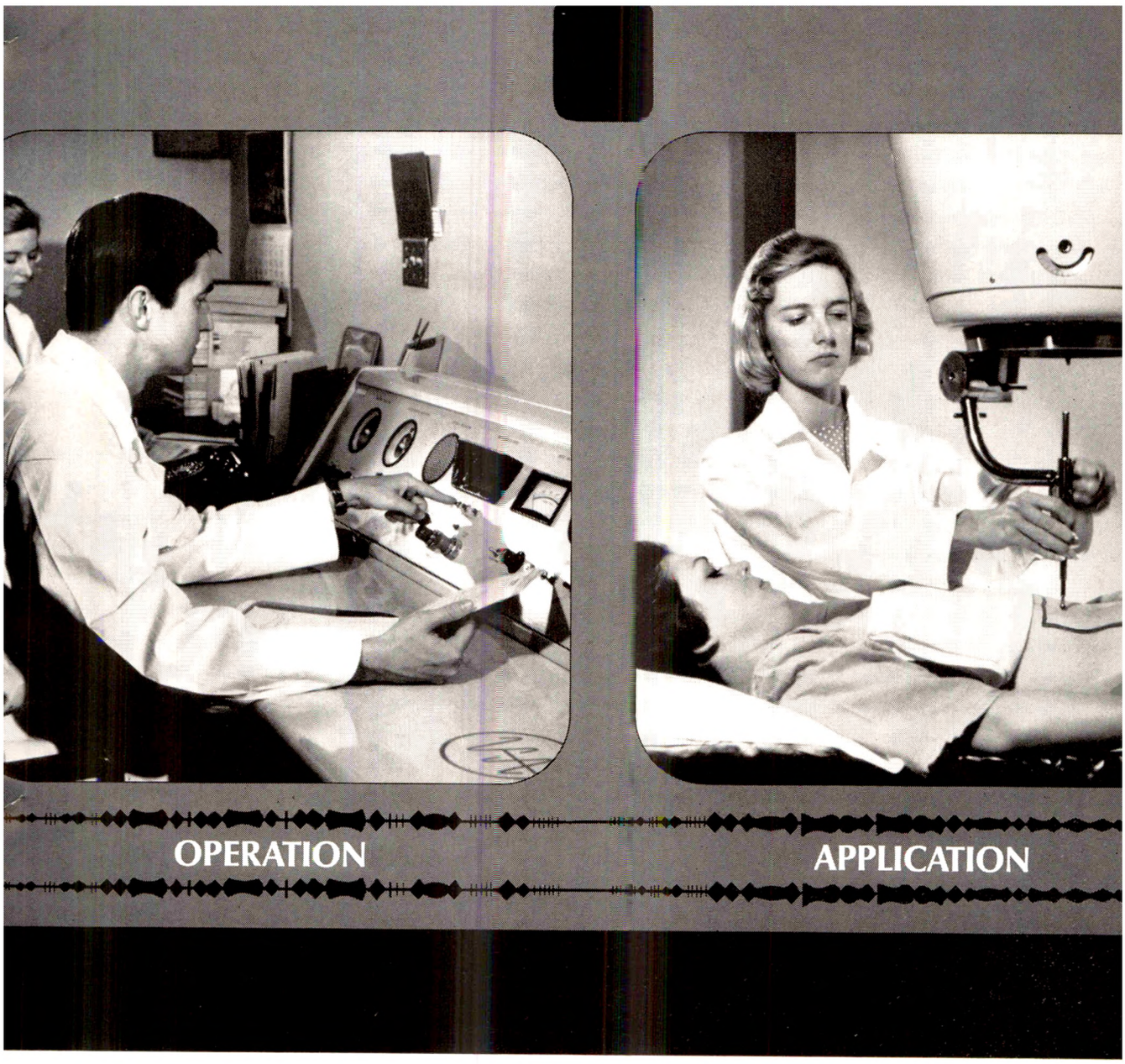
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- **Varian patient support assembly speeds positioning and treatment for greater patient convenience and more efficient system use.**
- **Greater than 350 rad/min/meter, flattened to ±3%... focal spot is less than 3 mm. Leakage radiation outside main cone is less than 0.1% of central axis intensity.**
- **X-ray head has beam-defining jaws which move**



SEE THE VARIAN 6 MEV CLINAC® IN ACTION

on arcs subtending the target and provide a wide range of field sizes, from zero to 27x30 cm at 1 meter, with rounded corners.

■ Rotates 360° about the horizontal axis, while maintaining 1 meter between the target and the isocenter. No floor cutouts are required. Total variation of X-ray field flatness is maintained with ±3% during 360° machine rotation.

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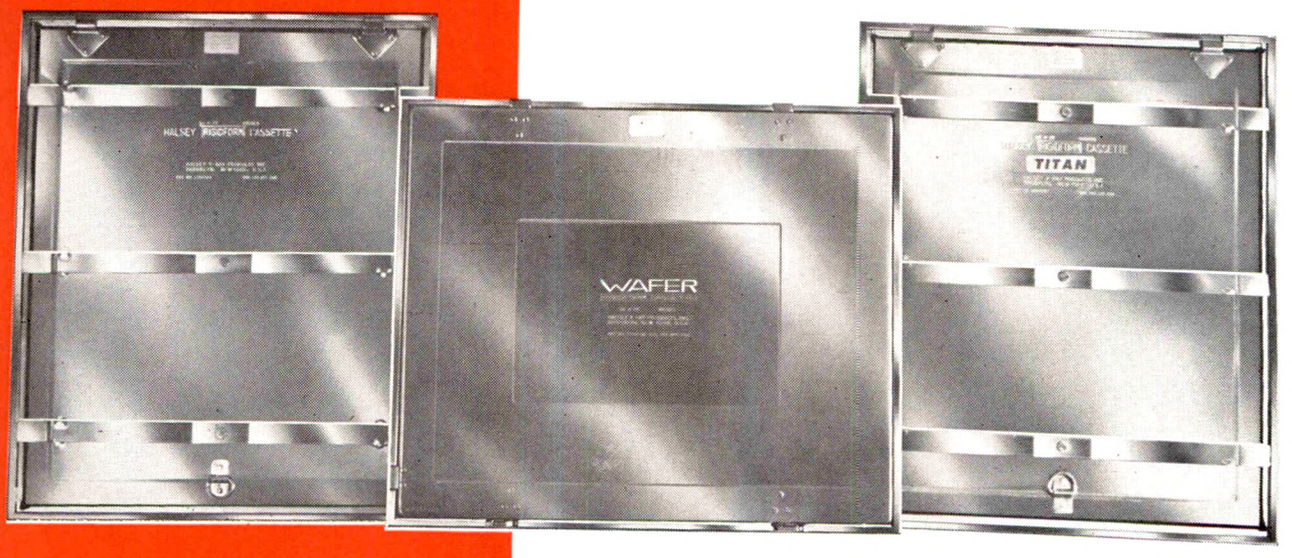
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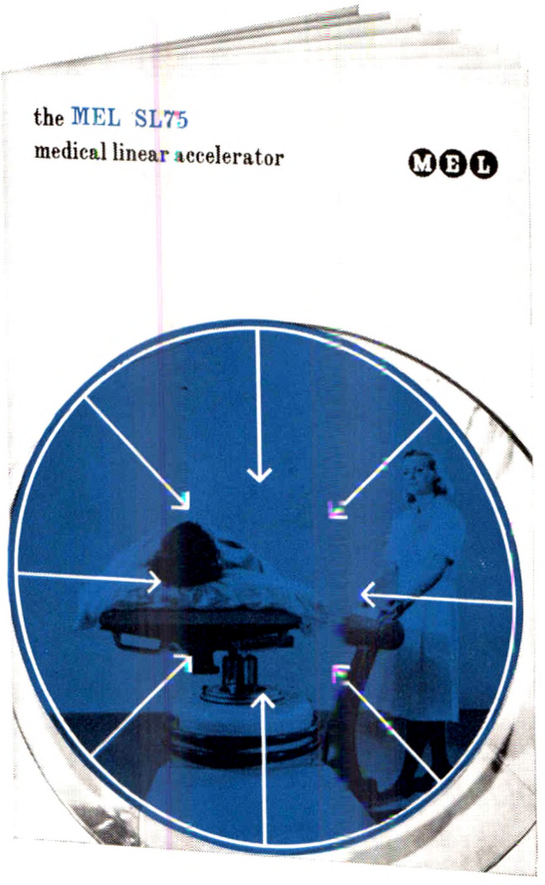
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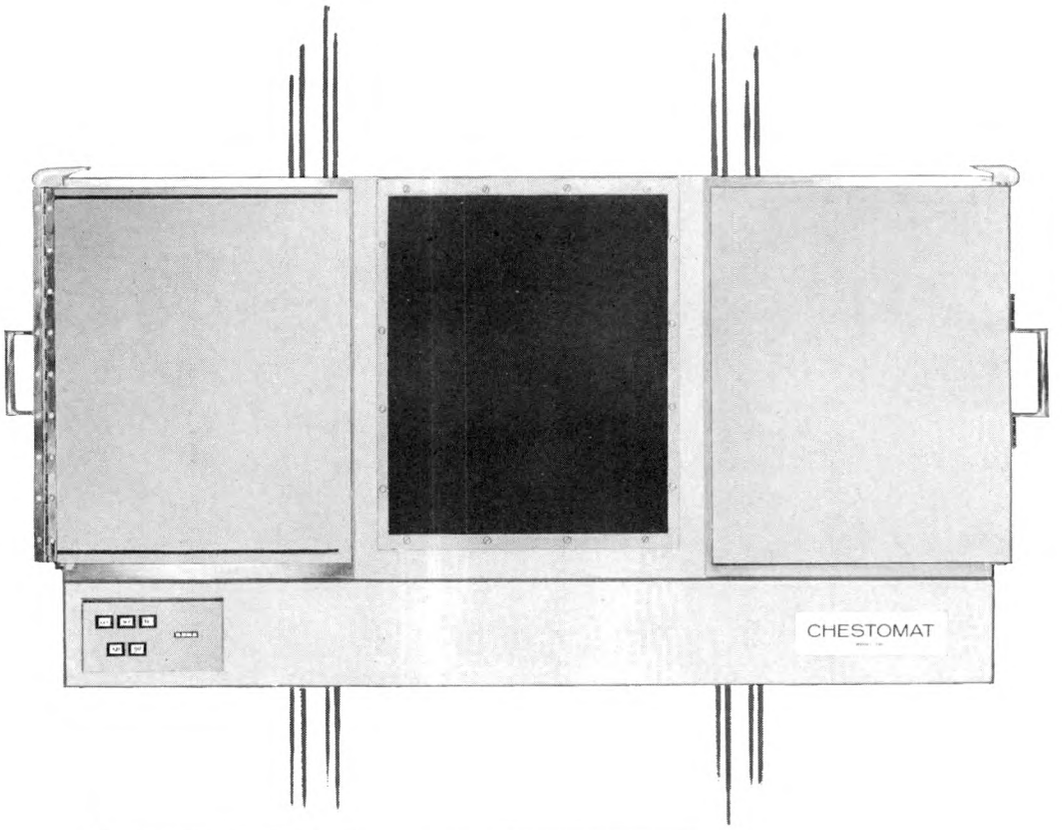
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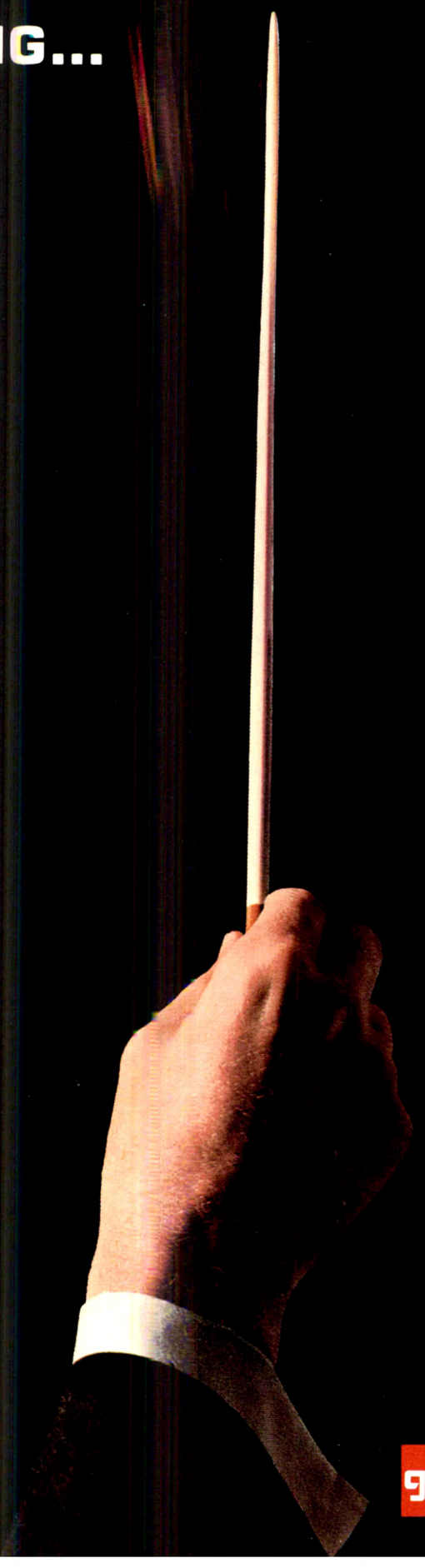
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TRENDS IN THE MANAGEMENT OF THE CANCER PATIENT*

THE PRESIDENT'S ADDRESS, 1966

By JUSTIN J. STEIN, M.D.
LOS ANGELES, CALIFORNIA

THE SOCIETY

IT HAS been a great honor for me to be president of the American Radium Society during the time of its fiftieth anniversary.

This Society was founded in 1916 when in June of that year "some 24 physicians interested in the subject of radium held a meeting at the Ritterhouse Hotel in Philadelphia, Pennsylvania, Thursday, October 26 at seven o'clock."[9] After deciding that such a Society was greatly needed, it was agreed that a constitution and bylaws should be adopted. A Canadian internist, W. H. B. Aikens, was elected the first president. The AMERICAN JOURNAL OF ROENTGENOLOGY was made the official organ of the Society at the Fifth Annual Meeting, April 26, 1920, with Dr. Henry K. Pancoast presiding.[3] Two years later "Radium Therapy" was added to the title of the AMERICAN JOURNAL of ROENTGENOLOGY and in 1952 the term "NUCLEAR MEDICINE."[9]

Dr. Brown,[6] in his Presidential address in 1962, described the objectives of the Society. He commented that "Throughout its life the American Radium Society has been a meeting ground for those whose interests have as a common denominator the study of malignant disease and the agents most effective in its treatment with particular attention to radium, x-ray and other sources of ionizing radiations. This is not a radiological society, not a surgical society, but an interspecialty organization. Furthermore, it has remained small enough so that many of the members know each other personally and welcome the annual meetings not only for the scientific programs but for the opportunities which they present for exchange of ideas informally between individuals or in small groups."

The objectives of this Society (after modification of the original objectives in the constitution in 1950 and again in 1961) are now stated as follows: "The objectives of the Society shall be to promote the scientific study of radium and other sources of ionizing radiation in relation to their

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
From the Department of Radiology, UCLA Center for Health Sciences, Los Angeles, California.

physical properties, their biologic effect, and their therapeutic application, and to encourage liaison between the various specialties concerned with the treatment of cancer."[4]

The American Radium Society is really the only true oncological or cancer society in the United States whose members represent all the various specialties and related sciences which are actively engaged in cancer diagnosis, treatment, and research.

There is a tendency for specialty groups to form their own oncology organizations. There never has been a greater need for a single oncological or cancer organization because of the high degree of political, emotional and scientific interest in cancer which exists today. This Society fills a great need and provides a broad base for balance, stability, progress and for future growth for all physicians and scientists interested in cancer.

No one individual can know all that needs to be known about cancer. Teamwork is essential. Surgery and radiation therapy are not competitive. Consultation between the various specialists and help from the radiobiologists and from all scientists involved in cancer research is constantly necessary. If every member and officer of this Society will do his or her utmost to provide effective leadership and vision, this Society will remain pre-eminent in its chosen field and will be a credit to the medical profession. It will also be ready and willing to make specific recommendations to the Federal Government which, hopefully, would provide safeguards for the public and the medical profession.

THE CANCER PROBLEM

With the continual increase in number and in the aging of the population, it is anticipated that the number of individuals with cancer will increase. Cancer is the number one cause of death from disease in children, and the second most common cause of death in this country, with 16 per cent of all deaths attributed to it. One in every 4 Americans who are now living will probably develop cancer at some time during their lifetime and 1 of 3 patients with cancer can expect to be cured by the proper use of present treatment methods. The socio-economic impact of cancer is tremendous with a high percentage of individuals afflicted during their productive years. The annual cost of cancer in this country has been estimated to be in excess of 11 billion dollars.

INFLUENCE OF THE GOVERNMENT

It should be emphasized that during the past 3 decades more progress has been made in the diagnosis, treatment and in the understanding of cancer than in all previous times.

Many noteworthy trends or changing concepts with regard to the actual management of patients with cancer as well as in the philosophical approach are taking place. The President of the United States has singled out heart disease, cancer and stroke for special consideration because 71 per cent of all deaths are caused by these three conditions. Based on the actual comparison of American standards of medical practice and of achieved performance by physicians, no clear mandate exists to demand or require a complete overhaul of the practice of medicine.

It is understandable that the medical profession should view with apprehension and with some degree of alarm the tremendous changes envisaged in the practice of medicine which will be forthcoming if the aims of the recently enacted federal legislation are fulfilled. Fortunately, the impact of the heart, cancer and stroke legislation will not occur simultaneously with the start of the Medicare program. Later there will be considerable overlapping of the two programs. Whether the medical profession approves or not, it seems quite certain that the present administration in Washington will vigorously pursue the revolutionary trend for governmental support for health affairs.

The government's projected program of regional medical centers to fight heart

disease, cancer and stroke has dramatically and sharply focused attention to the regional medical concept of centers for special diseases.

The aims of the regional medical program are good. If—as the law clearly states—a regional program will not interfere with existing patterns of medical practice, then some good can come from such a program; also, if the government provides only financial support and does not attempt to direct the actual medical management of patients.

If the local areas and regions can have better biomedical libraries, an improved and expanded continuing medical education, research and training, and adequate patient facilities, this will result in the community physician being better informed and able to provide more enlightened services to his patients. He will be able to learn about medical advances much faster and he will know how highly specialized treatment or diagnostic procedures can be made quickly available for his patients.

I am certain that everything possible has not been done to speed up communications between laboratory scientists engaged in medical research and the practicing physician in order that the latest advances can be made available to medical centers, clinics and to the community physician.

The establishment of regional centers of a highly sophisticated type for the diagnosis, treatment and research in cancer will serve a most useful purpose in any regional program.

It is not envisaged that all cancer patients would be treated in such a center. Cancer patients presenting special problems in diagnosis and treatment, patients with rare types of cancer, and patients being treated under combined programs, such as by the use of radiation therapy and chemotherapy or surgery, would be eligible for admission to such a center. Specialized diagnostic techniques, such as lymphangiography, thermography, mammography, *et cetera*, could be evaluated.

The cost of radiation therapy equipment is very high. It is unfortunate to see so many cobalt 60 therapy units being installed in small hospitals which have neither an adequate patient load nor qualified personnel. All hospitals do not have intensive care units for coronary heart disease patients, open heart surgery, or neurosurgery facilities. The centralization of radiation therapy equipment and qualified personnel is essential for the future. It is not sound medically or economically for every medical facility to treat cancer and, especially, patients with early cancer. The establishment of radiation therapy centers will do much to facilitate the proper use of ionizing radiation and allow for the further development of the specialty of radiation therapy.

The regional medical program will do much to elevate the standards of all hospitals, large or small. Better usage of beds and treatment facilities will also be made. Approximately 60 per cent of all hospitals in the United States have 100 beds or less and 85 per cent of all patients with benign and malignant neoplastic disease are treated in community hospitals that are not affiliated with medical schools.[11] Stetson,[14] in 1964, stated that "While it is true that we are making progress in our many excellent oncologic centers, where specialized equipment and personnel are available, there are many rural, suburban, and urban areas in which the management of the cancer patient leaves something to be desired." He stressed the need for community planning for the care of the patient with cancer and also of the need for the development of specialized cancer facilities.

The creation of specialized hospitals has not been widely accepted in the past. It is highly plausible in my opinion for a cancer or oncological institute to exist under the structure and guidance of a general or broadly oriented medical center. The different specialty departments of the university or medical center could staff and direct the specialized activities of the cancer hospital or institute. The interns

and residents could be rotated through the specialized center in order to provide them with a broad training. The specialty institute should be organized with full local and community support and responsibility and it should not be in competition with existing medical facilities.

It is practically impossible to enlarge or expand the medical activities in many existing structures without completely disrupting teaching and research activities and on-going medical programs.

The newly proposed regional centers do not have to be grandiose in size. Their main functions would be to provide specialized training, to develop and evaluate new techniques for diagnosis and treatment, to manage patients presenting special problems, provide special education for the community physicians, and to cooperate closely with all voluntary, local, state and federal agencies engaged in health activities. If the needs of the community and region are carefully evaluated, the duplication of expensive equipment and of medical personnel will not be necessary. One of the greatest existing needs is for the sound community-wide planning of all health facilities and services. It is urgently necessary that more paramedical health personnel be trained who can assume greater responsibilities in the care of patients.

The existing specialized cancer hospitals and institutes and research centers have certainly contributed a great deal to our present knowledge of cancer diagnosis, treatment and research. They have also been actively engaged in giving postgraduate education to physicians, scientists, and paramedical personnel.

The participation by the practicing physician is essential for the success of any regional program. Practically every day one sees the desirability for the services of a local physician to help in the over-all management of patients with cancer.

Farrow,[7] in 1965, commented on the increasing interest of the federal government in the cancer problem. He also stated that "to date most of the progress in treatment and actual care of the patients with cancer has been very little dependent on government funds." He stressed the necessity for the formation of a joint committee which would be truly representative of all the specialties and organizations which are most active in the diagnosis and treatment of cancer. Such a joint committee, after thorough study and unified action, would be able to provide the much needed advice and recommendations, when appropriate, concerning the distribution of federal funds.

The federal government and money will not solve all medical problems nor eradicate all diseases. There will always be the need for dedicated, highly motivated individuals with vision, energy, perseverance, and high ideals, working in an environment where freedom to try and to think is possible.

We must beware that too much bungling inefficiency and haste by the federal government will discourage highly qualified individuals from entering the medical profession. This will not occur if the advice of practicing physicians and of leaders in the medical profession is sought and if these physicians see to it that their voices are heard.

The frequent re-evaluation of the participation by the government in health matters by non-governmental physicians will help provide safeguards for the public and the medical professions against inefficient bureaucratic health programs.

USE OF CLINICAL TRIALS

The need for well-designed clinical trials with randomization of patients has been clearly established. In recent years, the increased interest by many different specialists has stimulated greater interest in clinical trials. Chemotherapy and megavoltage radiation therapy have provided the impetus for more clinical trials.

It is certainly reasonable to anticipate that carefully planned protocols for clinical trials carried out under adequate medical

safeguards can be most productive in providing badly needed information. Clinical cancer research has not been as vigorously pursued as it should be. Millions of dollars have been spent on research on animals and fruit flies and rightly so; however, the patient with cancer affords tremendous opportunities for carefully planned and supervised clinical research. Much of the diagnostic and therapeutic work which is done on patients represents clinical research. It only becomes useful and meaningful if adequate records are kept of what was done and what occurred and under rigid criteria for patient selection.

There are many problems in which clinical trials have been or can be helpful as, for example, in determining the value of preoperative radiation therapy for lung, bladder, and head and neck cancer. Will combinations of therapy, such as 5-Fluorouracil and radiation therapy given preoperatively, materially increase the 5 year results in the treatment of bladder cancer? Is simple mastectomy plus radiation therapy as effective as the radical mastectomy with or without radiation therapy? What is the most effective therapy for Stage 1 Hodgkin's disease or lymphosarcoma localized to one chain of lymph nodes in one side of the neck? Should lymphangiography be done routinely in all such patients? Should patients with operable endometrial carcinomas receive preoperative radiation therapy? Is chemical perfusion of the lower extremity necessary in all patients with operable Stage 1 malignant melanoma? Is removal of the inguinal lymph nodes, when not enlarged to palpation, routinely indicated in such cases? How much does chemotherapy and/or prophylactic inguinal lymph node surgery add to the 5 year results in such cases? We all have opinions on the above and on other problems, but how much precise scientific information is available based on truly randomized studies in series of cases whose scientific data are truly comparable?

If 85 per cent of the patients with cancer are managed in community hospitals not affiliated with medical schools, how can large enough series of patients representing the various forms of cancer be treated and the data compiled in a reasonable period of time?

THE PATIENT

More attention is being given to the complete medical status of the patient with cancer and not just concentration on the treatment of the malignant lesion. The majority of the patients will probably be in the older age groups who will usually have 2 or more medical diseases, the treatment of which must not be neglected. Some will have diabetes mellitus and cardiovascular disease or renal disease or a neurological problem, or other diseases.

The prompt correction of electrolyte imbalance and of the anemias, the institution of a proper diet and the recognition of potential complications will do much for the patient.

It is essential that the radiation therapist have hospital beds at his disposal. Occasionally, it may be necessary for him to hospitalize a patient for short periods of time. The radiation therapist is first a physician and secondarily a specialist in therapeutic radiology. The fullest use of the art of medicine as well as the use of scientific methods must be made. We often do not listen carefully enough to the patient's history nor do complete enough examinations of the patient. When we listen to the patient and thoroughly examine the patient, we learn more about the patient and are in a better position to manage the patient's total requirements. Since approximately 5 per cent of patients with cancer may have multiple internal malignancies, this possibility must be kept in mind.

THE ONCOLOGIST

It has been thought by some physicians that the training for an oncologist should be such that by virtue of his training he could be competent to do pathology, surgery and radiation therapy for the cancer

patient. It is possible for an individual to become proficient in several specialties and to keep abreast of the times, but it is difficult and not practical or realistic for the same physician to do both surgery and radiation therapy. If he is busy in the one specialty, he will not have time for the other. The more reasonable concept for an oncologist is one who specializes in the diagnosis and treatment of malignant tumors but who devotes his full time to either surgery or radiation therapy or cancer research or some other aspect of the cancer problem. One can be trained as a surgeon and then go into radiation therapy, but should not continue to do surgery. Many British radiation therapists have also been trained in surgery. Surgical training provides an excellent background for the radiation therapist and enables him to select more completely the best method of therapy or therapy combinations.

CHEMOTHERAPY

Perhaps the greatest benefit which has come out of the extensive and expensive nationwide chemotherapy program has been the stimulation of many individuals trained in different medical specialties to work as a team and to take more interest in the cancer patient. The internists and the hematologists have certainly taken a renewed interest in cancer. Our greatest hopes for chemotherapy have not materialized as yet and much indiscriminate use has been made of chemotherapeutic agents. Surgery and radiation therapy are not the answer to the patient with cancer and, ultimately, specific chemotherapeutic agents or combination of agents may be found which will be effective in controlling different types of cancer. To date, the choriocarcinoma is the only one which can be successfully controlled by chemotherapy in a high percentage of cases.

THE PREVENTION OF CANCER

In the future major efforts will be concentrated on the prevention of cancer. It is not necessary to know the precise etiology of a disease to be able to prevent it. There are many factors which play a role in the etiology of the different types of cancer. For a given individual, the cellular change from the normal to malignant may have been induced by a hormone, virus, chemical or by physical agents acting singly or in combination on the hereditary mechanism of the cell. It is quite possible that malignant change may occur by direct cellular action as well as by influencing a cell which has a predisposition to the development of cancer.

Sufficient data have accumulated to indict cigarette smoking as causally related to lung cancer. If cigarette smoking could be eliminated, it is quite possible that a majority of the cases of lung cancer could be prevented. The use of routine proctosigmoidoscopy and colon x-ray examinations in individuals over 35 years of age in both sexes would accomplish a great deal in the early diagnosis of cancer of the rectum, recto-sigmoid, and colon. Approximately 75 per cent of all benign rectal and colon lesions occur within reach of the finger or within sight of the eye through a proctosigmoidoscope. Cancer of the rectum and colon is the most prevalent of all neoplasms in the United States because it occurs in a high percentage of both sexes.

Avoidance of exposure to excess sunlight to prevent skin cancer; use of good oral hygiene and avoidance of alcohol to help prevent oral cancer; periodic cervical cytology to detect carcinoma *in situ* of the uterine cervix; and avoidance of atmospheric dusts and chemicals which may produce lung or bladder cancer are but a few of the preventive measures which may be taken.

CONTINUING MEDICAL EDUCATION

The half life of one's medical knowledge is about 10 years. Without a continuing medical education program, the physician who was once well trained will quickly fall behind in his medical knowledge. In fact, a cursory look at certain specialty scientific programs of today as compared to only 5

years ago will reveal enormous changes in medical diagnosis and therapy. The perennial problem in education is how to reach the physician in practice who does not go to regular hospital staff meetings, specialty scientific meetings, or take postgraduate courses.

There has been too much emphasis on "publish or perish" in the medical schools and too little thought of recognition given to the physician who is a highly competent stimulating teacher. Just because an individual is a highly capable researcher is no indication that he may be an effective teacher. Often it is difficult to find both capabilities in the same individual.

Much of the teaching in the preclinical and clinical years of medical schools could be done by the use of practicing physicians from the community. Too often medical school teaching is done by candidates for degrees and by individuals who have little concept of the actual practice of medicine. Continuing medical education will be a major factor in the heart, cancer and stroke program. It will have to be effectively organized in order to not only provide for the major medical centers but also to reach the community physicians and those physicians who are not participating in on-going programs. New techniques in education and the streamlining of present methods of education will be required.

NUMBER OF PHYSICIANS

There is no short cut to the proper education and training of physicians. A program designed to expand the number of educational facilities and to increase the number of excellent medical school candidates should have preceded the institution of vast governmental health programs which will only increase the dilemma of the shortage of physicians, dentists, nurses and of other health personnel.

For many years, the policies for the recruitment and education of medical students has been inadequate and short sighted. The best illustrative example has been the fact that over 25 per cent of all the interns and residents in the United States have been educated in foreign countries. Foreign medical school graduates (other than Canadians) made up 39 per cent of the total who passed medical licensure examinations in the United States in 1962. In 1961 the proportion was 36.7 per cent. In 1959 when the United States medical population was 237,395 there were 20,159 foreign medical graduates, including Canadians, practicing in the United States.[13] Foreign physicians have contributed greatly to American medicine and are welcome but why should this great nation not be capable of producing enough physicians to meet its own population needs?

In 1965 there was a total of 292,088 physicians in the United States and its possessions; of this total number 180,752 were in private practice and the remainder were in intern, residency, fellow or full-time hospital training programs, laboratory medicine, preventive medicine, administrative medicine, full-time medical school faculty, in research, retired, and not in practice.[1]

American medicine has reached its present state of excellence and its recognized medical position in the world because it has had the proper leadership and the freedom to excel. If research activities are curtailed and the physician is placed under too many restrictions, excessive paperwork and nonmedical requirements interfering with his practice, the standards of medicine will quickly deteriorate and fewer excellent students will seek medicine as a career.

STAGING OF CANCER

Considerable progress has been made by the World Health Organization, the International Union against Cancer, and the American Joint Committee to develop acceptable methods of staging of certain types of cancer.

It has always been difficult to try to compare published scientific data because often the data are not comparable. If a uniform world-wide method of staging is agreed upon, then a comparison of the re-

sults of different methods of therapy will become more meaningful.

The American Joint Committee on Clinical Staging and End Results Reporting has completed 6 fascicles as follows: Fascicle 1, Breast (2 editions); Fascicle 2, Larynx (2 editions); Fascicle 3, Reporting of Cancer Survival and End Results; Fascicle 4, Cervix; Fascicle 5, Corpus Uteri; and Fascicle 6, A Clinical Staging System for Cancer of the Pharynx. Other fascicles are in various stages of completion.[2] The wide acceptance by American physicians of the TNM (tumor, lymph node, metastasis) system of classification will do a great deal toward making comparative studies possible when the effects of different types of treatments on cancer patients are being studied.

EPIDEMIOLOGY

Epidemiology is a most fascinating study. It will receive greater support and attention and new problems will be assigned to the epidemiologists.

Levin[8] has defined epidemiology "... as the study of the relation of disease occurrence in human or other populations with factors or events that may be of significance from the standpoint of causation, prevention or control of the disease."

A great deal of evidence is being accumulated concerning the etiologic and preventive aspects of the different types of cancer. The human being is constantly exposed to a multiplicity of events, such as the effects from industrial carcinogens, air pollution, smoking, food and food additives, and to natural and man-made radiations. The intrinsic and extrinsic effects must be studied. There is much to be learned about etiologic factors in the causation of cancer of the breast, colon and rectum, uterus, oral cavity, lung and skin. It is estimated that about 60 per cent of all cancer deaths are caused by cancers involving these organs.

It is interesting that in those countries where cancer of the stomach is a prominent cause of death there is a relatively lower incidence of colon and rectal cancer. In the United States, cancer of the stomach is steadily decreasing for no known reason and colon cancer is increasing but not rectal cancer. Epidemiologic surveys have linked cigarette smoking to lung cancer; also have shown that males who usually smoke cigars or pipes (Jews) have a much lower incidence of lung cancer than do Catholic or Protestant males who are inclined to cigarette smoking.[12] The study of cancer among different ethnic groups, isolated groups of individuals with little contact with other parts of the world, religious groups with different habits, and of specific types of tumors peculiar to certain regions, *et cetera*, has contributed much to our knowledge of cancer and such studies must be continued.

RADIATION THERAPY

The trend in radiation therapy is for the separation of radiation therapy or therapeutic radiology from diagnostic radiology; toward the use of megavolt x-rays and electrons; greater understanding of radiobiology and radiation physics; the centralization of equipment and establishment of radiation therapy centers; the use of combined modalities (*e.g.* preoperative radiation therapy combined with surgery, and of radiation therapy combined with chemotherapy and surgery); and to challenge preconceived "statements of fact" as dogma. Investigations will continue to study the effects of irradiation under increased oxygen tension and under conditions of hypoxia. The search will be continued to find nontoxic radioprotective agents and factors which will increase the effectiveness of the radiation response. We have a long way to go but the horizon is now in full view rather than only being dimly visible as it has been for so many years.

Clinical investigations in time dose relationship must be continued. Is 6,000 rads tumor dose in 6 weeks the ideal treatment

for most squamous cell carcinomas? Will the "split-dose" technique give better results? Is prolonged fractionation with higher dosage superior? Are treatments given at 48 and 72 hour intervals just as effective as when administered 5 or 6 times weekly? The delivery of the required tumor dose over a long period of time (from 4 to 18 weeks) has certainly reduced the morbidity and the number of complications and has decreased the effect on the vasculoconnective tissue.

Andrews[5] has stated that "If, therefore, optimal patterns of dose and time relationships are to be found for a variety of clinical cancer situations, then definitive studies of their relationships must be undertaken systematically by the deliberate formulation of joint, cooperative, controlled large scale trials on a carefully elaborated clinical research protocol basis."

There can be suggested radiation therapy guides as to total dosage for certain types of malignant tumors, but the treatment of an individual case will often present problems before, during or after therapy that will tax the experience and judgment of the radiation therapist responsible for his medical care. There will be some standardization of therapy but always only to a degree.

Stetson[14] has pointed out the need for radiation therapy centers because of the expensive equipment and qualified personnel necessary and for the prevention of the duplication of equipment in a community. The patient with curable cancer will have the best opportunity to obtain a good result when radiation therapy centers which are well-equipped and with adequate personnel both in the clinical and investigative fields are established.

Real progress in radiation therapy will be made when there are many straight radiation therapy training centers, more radiation treatment centers established, and when the training of radiation therapists is separated from diagnostic radiology.

The fact is not fully appreciated that, in malignant tumors which are potentially curable, for 50 per cent of the cases surgery will be the treatment of choice and in approximately 40 per cent radiation therapy.

CONCLUSION

Patterson[10] in discussing current medical and surgical problems quoted Berry as follows: "How to marshal more rapidly, for the benefit of mankind, the results of new knowledge; how to provide better care, more equitably distributed; how to create a more fruitful environment for teaching and research; how to utilize in the national interest the vast resources of government and yet safeguard essential independence." These were the problems of yesterday; they are the same today; and will be the same tomorrow. The federal government and the public are becoming increasingly sophisticated with regard to health and greater demands will continue to be made for increasingly high quality medical care which is readily available at a reasonable cost. The medical profession must not only keep abreast of the changing times but must, in reality, anticipate and plan for and help direct the future medical needs of the American public.

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THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK WITH METHOTREXATE AND IRRADIATION*

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DURING the past 5 years, 150 squamous cell carcinomas of the head and neck in 132 patients were treated with a combination of methotrexate and irradiation.[1,3] Based on this experience, some opinions of the effectiveness of this combined therapy are offered.

Early in the study, methotrexate was administered by continuous intra-arterial infusion. However, because of the technical difficulties and serious complications, infusion was discontinued and thereafter the drug was given by mouth. The current procedure is to give a daily dose of 7.5 mg. methotrexate by mouth for 1 to 2 weeks and then add irradiation. When the drug is very effective and the tumor shrinks markedly, the chemotherapy is maintained for 3 or 4 weeks if tolerated, in order to get maximum tumor shrinkage from that modality. In the latter weeks, the daily dose is occasionally reduced to 5 mg. This sequential technique permitted evaluation of the effect of the drug alone. It also permitted increase or decrease of its dose in accordance with the response of the tumor and the reaction of the normal tissues.

The following 3 cases illustrate many features of combined therapy.

ILLUSTRATIVE CASES

CASE 1. M.R., a female aged 67 years, was seen on November 19, 1963 for an extensive squamous cell carcinoma of the left side of the oral tongue of 4 months' duration. It was staged T3 No (Fig. 1). Methotrexate orally, 7.5 mg. per day, was given for a total dose of 55 mg. in 7 days. On Day 7, the tumor had shrunk 75 per cent in volume (Fig. 2). Because the tumor disappeared, the patient refused the additional treatment with interstitial radium needles. She returned 2 months later on January 31, 1964, because the tumor had recurred to its original size (Fig. 3). A second course of oral methotrexate, 82 mg. in 11 days, produced a 90 per cent shrinkage of the tumor (Fig. 4). On the 12th day, radium needles were inserted for a

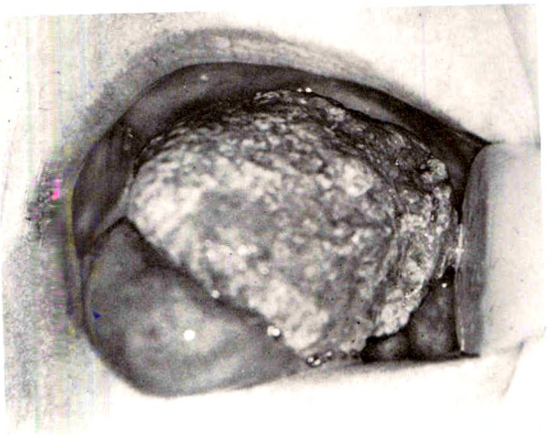


FIG. 1. Case 1. *November 19, 1963:* Squamous cell carcinoma of the oral tongue before treatment.

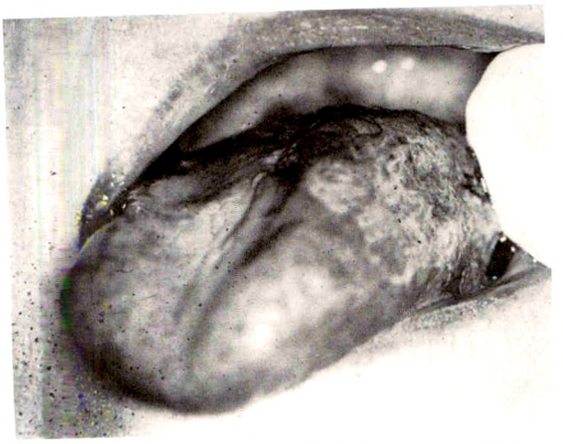


FIG. 2. Case 1. *November 26, 1963:* Appearance on seventh day. Total dose of methotrexate was 55 mg. in 7 days. Tumor shrank more than 75 per cent. Patient subsequently refused proffered radiation therapy.

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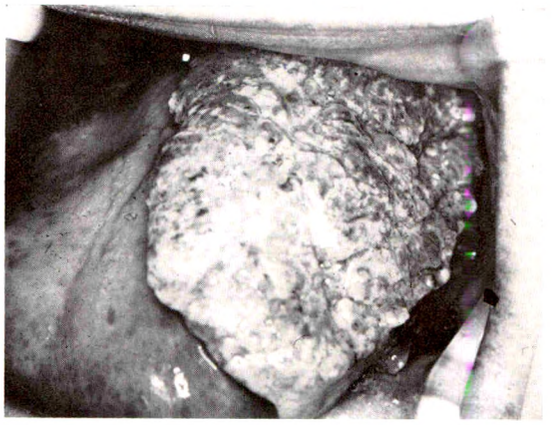


FIG. 3. Case 1. *January 31, 1964:* Two months later, tumor had recurred to original size.

tumor dose of 8,800 rads in 3 days. The tumor disappeared and has not recurred to date (Fig. 5).

Five months later, a second small carcinoma of the opposite lateral margin of the tongue responded similarly to methotrexate and interstitial radium. Ten months later, a third carcinoma appeared on the untreated dorsum of the right side of the tongue, and was excised. There is no recurrence of any lesion to date, almost 3 years after the first treatment.

Comment. This case illustrates marked chemosensitivity even to a second course of oral methotrexate. Fifteen per cent of all lesions show this type of marked shrinkage (Table 1). The drug alone, although very effective, characteristically failed to produce permanent control of the tumor, and had to be supplemented with radium for 2 lesions, and surgery for the third.

CASE II. E.B., a male aged 62 years, had an emergency tracheotomy for a massive intrinsic carcinoma of the larynx (T_4 No) of 1.5 years' duration (Fig. 6). By mistake, the patient was at first given twice the usual daily dose of oral methotrexate for 5 days, *i.e.*, 15 mg. daily, and thereafter the dose was reduced to 7.5 mg. daily for 12 more days. The total dose was 155 mg. in 17 days. It is noteworthy that there were no symptoms of toxicity. The tumor shrank 50 per cent by Day 7 and then the tracheal tube was removed. By Day 10, the tracheal stoma closed spontaneously; and on the same day 230 kv. x-ray therapy was started (Fig. 7). The total tumor dose was 6,160 rads in 33 days. The tumor disappeared on the last day of treatment and has not recurred. Today, almost 4 years after treatment, there is no evidence of disease, and the larynx functions with slightly reduced mobility of one wall.

Comment. This case illustrates several features: (1) marked chemosensitivity; (2) the ability of an occasional patient to tolerate large doses of methotrexate without undue toxicity; and (3) combined therapy is particularly effective when the tumor responds markedly to both modalities. This patient (Fig. 7) demonstrates the characteristically rapid rate of shrinkage of



FIG. 4. Case 1. *February 10, 1964:* Appearance of the recurrent tumor on the eleventh day, when the dose of oral methotrexate was 82 mg. Tumor shrank 90 per cent. Radium needles were inserted on the following day.

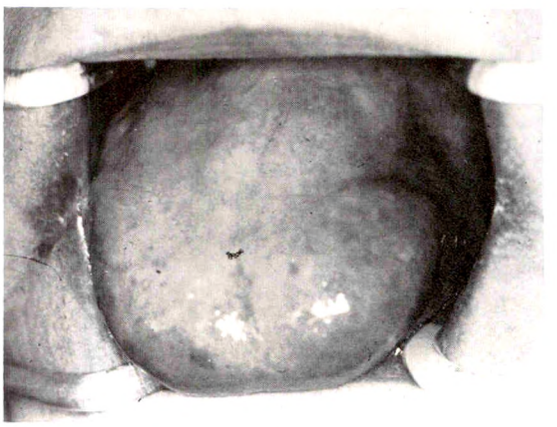


FIG. 5. Case 1. *April 7, 1964:* Appearance of tongue 2 months after radium implantation. This lesion has not recurred to date.

Table I

INITIAL SHRINKAGE OF PRIMARY TUMORS PRODUCED BY METHOTREXATE ALONE

Site	No. of Lesions	Per Cent Shrinkage					
		Favorable Responses				Failures	
		100 to 76	75 to 51	50 to 26	25 Certain	24 to 1	No Effect
Oral Cavity	18	4	1	10	1	1	1
Oropharynx	55	8	11	13	6	6	11
Hypopharynx	30	3	3	7	7	3	7
Larynx	22	4	4	5	2	2	5
Nasopharynx	17	1	4	1	1	2	8
Nasal Sinuses	8	1	1	3	—	1	2
Totals	150	21	24	39	17	15	34
		101/150 = 67%				49/150=33%	

a tumor that is markedly chemosensitive. Tumors which are extremely sensitive to irradiation shrink at a slower rate.

Case III. P.S., a male aged 53 years, had an infiltrating carcinoma of the pyriform sinus with symptoms of 4 months' duration. It produced complete fixation of the left wall of the larynx. There was a 2.3 cm. metastatic lymph node. It was classified T3 N1 (Fig. 8). Oral methotrexate therapy, 7.5 mg. per day, was carried to a total dose of 115 mg. in 16 days. On Day 22, the primary tumor shrank 50 per cent and the lymph node 40 per cent (Fig. 9). Irradiation with 2 mv. x-rays was started on Day 20, and continued to a total tumor dose of 6,700 rads in 40 days (Fig. 11). The primary tumor and lymph node disappeared before treatment was completed. Function was completely restored so that months later he was able to deliver a 1 hour sermon (Fig. 10). One year later, the tumor recurred to its original size, and in 2 months caused hemorrhage and death.

Comment. This tumor, like the previous one, showed rapid shrinkage from methotrexate, and disappeared before irradiation was completed. The fact that the tumor re-

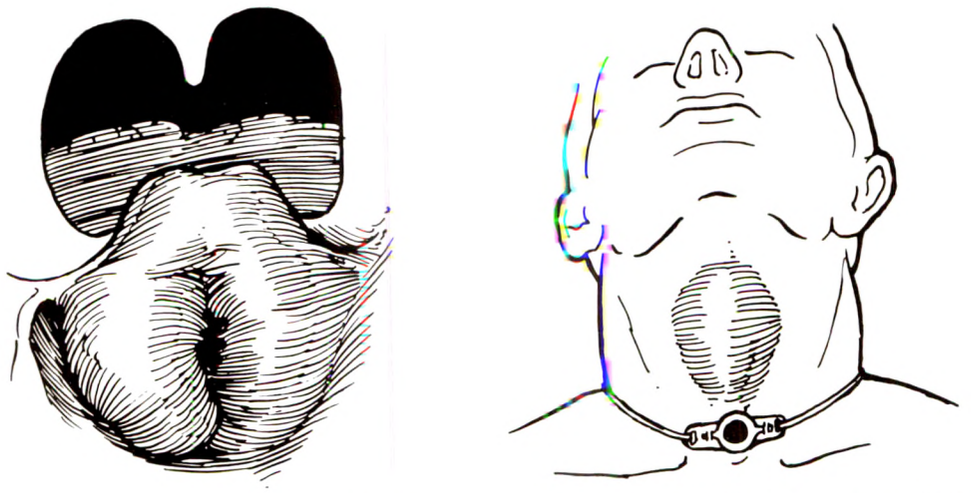


Fig. 6. Case II. Massive T4 carcinoma of the larynx (glottis) producing a visible bulge and causing laryngeal obstruction (relieved by emergency tracheotomy).

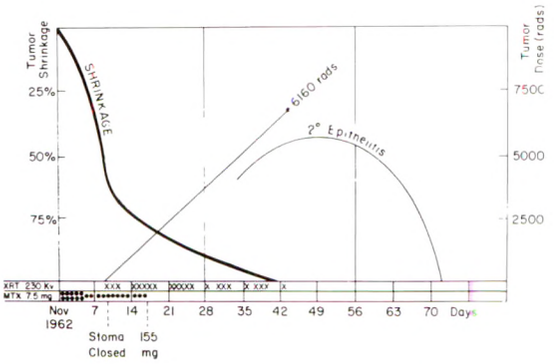


FIG. 7. Case II. E. B., carcinoma of the larynx (glottis), T4 No. Treatment and reaction chart. Through an error in execution of orders, the daily dose of oral methotrexate for the first 5 days was 15 mg. Thereafter, it was reduced to 7.5 mg. daily. On the tenth day, when the total dose was 105 mg., the tumor had shrunk 65 per cent, the tracheal stoma was closed, and x-ray therapy was started. Patient is free of disease more than 4 years to date. The epithelitis lasted somewhat longer than average as a result of combined therapy.

curred in 1 year was due to the presence of a small component of chemoresistant as well as radioresistant cells. This concept of *chemoresistance* will be discussed later in the paper.

The radiation epithelitis in this patient was unduly severe, because it was added to the previous methotrexate-induced epithelitis. This is additional evidence of the impact of combined therapy in this instance on normal tissues.

EFFECTIVENESS OF ORAL METHOTREXATE

The routine technique of giving a preliminary course of oral methotrexate permitted evaluation of the effect of methotrexate alone in 150 lesions (Table 1). When the tumor shrank more than 25 per cent in volume, the result was considered successful. Sixty-seven per cent of all primary tumors responded successfully. Within the successful group, 21 cases (14 per cent) were so markedly chemosensitive as to shrink from 76 per cent to 100 per cent in volume from methotrexate alone. This was illustrated in the 3 sample case histories. A

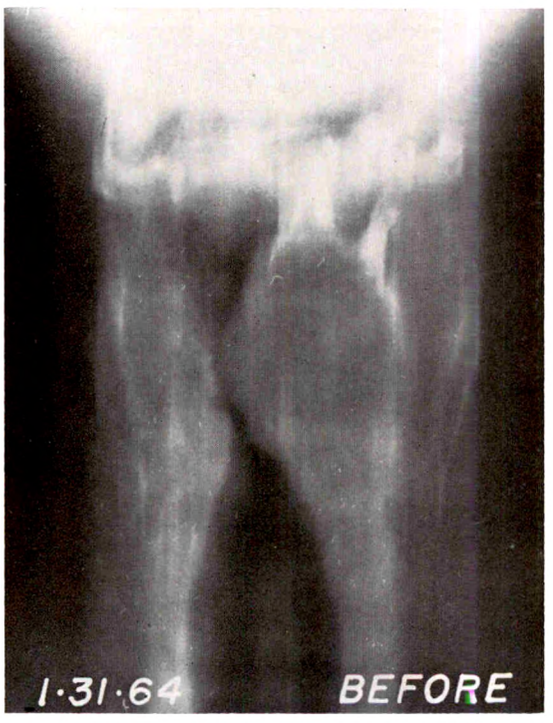


FIG. 8. Case III. Infiltrating carcinoma of the pyriform sinus, T3 N1, before treatment.

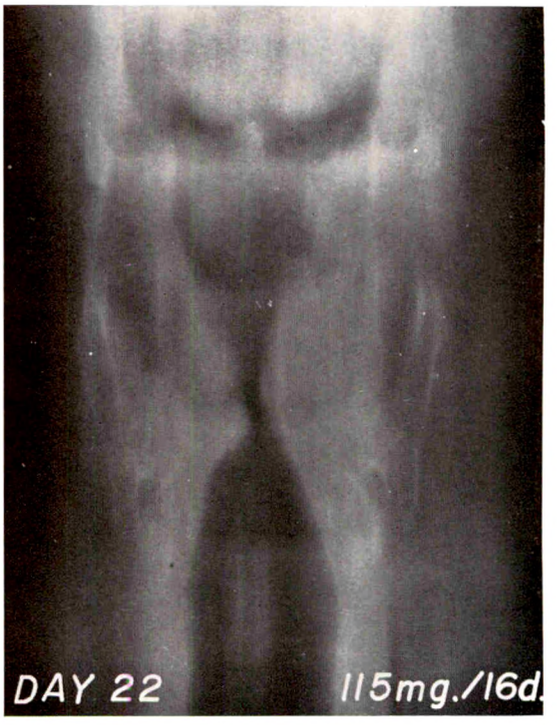


FIG. 9. Case III. Day 22. Approximately 50 per cent shrinkage of the primary tumor following 115 mg. methotrexate in 16 days. Irradiation was started on Day 22.

lesion which shrank less than 25 per cent in volume was called a failure, and there were 33 per cent failures. The category "25 per cent certain" comprises those lesions to which, as soon as they had shrunk 25 per cent, usually within 1 week, irradiation was added and both types of treatment were continued simultaneously.

These reported shrinkage rates are more favorable than the ones reported by the general chemotherapist. Our end-point of observation is the immediate shrinkage of the tumor, however transitory. The general chemotherapist, using the drug alone, seeks more prolonged shrinkage and increased longevity of the patient.

When the individual sites are examined, the frequency of favorable responses was 88 per cent in the oral cavity lesions and 65 per cent in all the other lesions, except nasopharynx which was 40 per cent (Table 1).

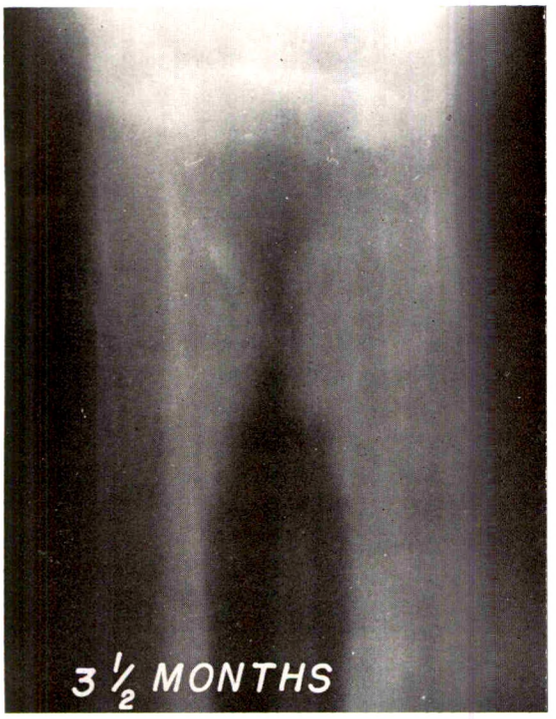


FIG. 10. Case III. Three months after methotrexate and a radiation dose of 6,700 rads in 40 days. The patient was able to deliver a 1 hour sermon. The response of the tumor to combined therapy was the same as in Case II, yet 1 year later, the lesion in Case III recurred.

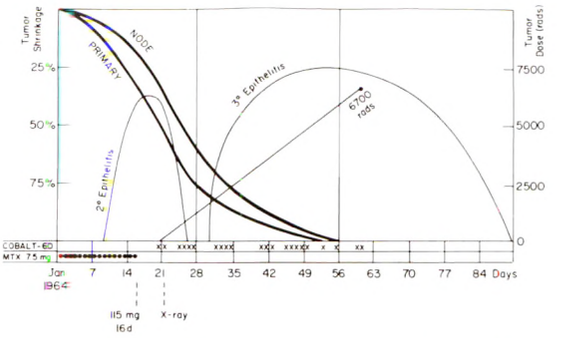


FIG. 11. Case III. P. S., carcinoma of the pyriform sinus, T3N1. Treatment and reaction chart. Note that on Day 20, when x-ray therapy was started, the primary tumor had shrunk 50 per cent in volume and the lymph node 40 per cent. Although the methotrexate epithelitis healed promptly, it intensified the radiation epithelitis which was more severe and prolonged than average. This type of intensified effect on normal tissue is rather common in combined therapy.

Metastatic cervical lymph nodes responded to preliminary oral methotrexate almost as well as the primary tumors (Table II). Fifty-seven per cent of all lymph nodes responded favorably. Eight lymph nodes (10 per cent) shrank from 76 to 100 per cent in volume. Best responses occurred in lymph nodes from the laryngopharynx (70 per cent), then oral cavity and oropharynx (60 per cent), and finally nasopharynx and nasal sinuses (30 per cent).

URINE EXCRETION STUDIES

Using tritiated methotrexate, it was found that 50 per cent of the drug was excreted into the urine within 12 hours (Fig. 12). When the kidneys function poorly, the methotrexate is not excreted but is recirculated and continues to exercise its effect. It is therefore dangerous to use methotrexate in patients with cardiovascular-renal disease, alcoholic cirrhosis and other debilitating diseases. Severe toxicity and even death could occur. In patients with constitutional disease, methotrexate therapy requires meticulous supervision, which is best accomplished in the hospital. The risks are warranted by the occasional favorable response.

TABLE II

INITIAL SHRINKAGE OF LYMPH NODES FROM METHOTREXATE ONLY

Site	No. of Lesions	Per Cent Shrinkage in Volume					
		Favorable Responses				Failures	
		100 to 76	75 to 51	50 to 26	25 Certain	24 to 1	0
Oral Cavity and Oropharynx	40	4	10	9	1	8	8
Laryngopharynx	23	3	2	9	2	2	5
Nasopharynx and Nasal Sinuses	16	1	1	3	—	3	8
Totals	79	8	13	21	3	13	21
		45/79=57%				34/79=43%	

The potency of the drug is remarkable. Only a small part of the administered drug is retained in the body, and it acts on a cancer cell during a small fraction of its lifetime. Yet it can produce marked destructive changes in many cancers.

EVIDENCE SUPPORTING COMBINED THERAPY

In earlier reports of this study,[1,3] 3 types of evidence supporting the beneficial effects of combined therapy were described.

1. Early in the study, the marked shrinkage produced by methotrexate was such that it was believed that only a sublethal dose of radiation would be required to produce a permanent lethal effect on the tumor. Thus, 1 group of patients received methotrexate plus a *sublethal* dose of x-rays. In Figure 13, the 2 curves and shaded area represent the published tumor *lethal* doses when irradiation alone is given.[4,6,7] Seventeen patients received methotrexate plus *sublethal* x-ray doses. In 10 of these patients, the tumor was destroyed. Irradiation alone, with these small doses, would have produced few or no arrests instead of 10 arrests. Hence, it is probable that methotrexate plus these sublethal doses produced a lethal effect. Seven other lesions were, at first, completely destroyed, but recurred many months later. These failures jeopardized the lives of the patients and consequently the sublethal dose tactic was discontinued. In subsequent cases, higher x-ray doses were given and the end-point was increase in the arrest rate (Fig. 20 and 21).

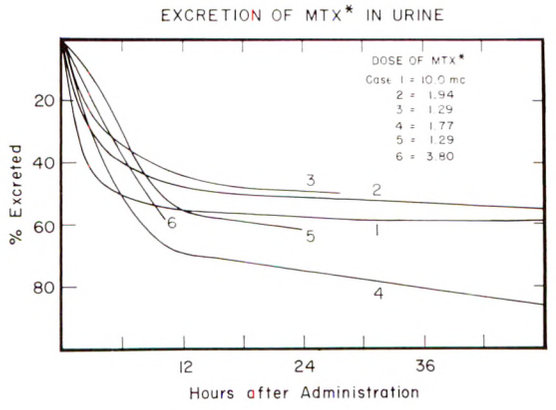


FIG. 12. Studies of excretion of tritiated methotrexate in the urine of 6 patients. Data are based on aliquots of urine collected continually at 4 hour intervals. Note that 50 per cent of the drug is excreted within 8 hours.

2. Another type of evidence, published previously,[3] was obtained when multiple metastatic cervical lymph nodes were present. One group of lymph nodes was treated with radiation alone and another group treated with the 2 modalities. Although this technique provided a good type of interior control, there were too few

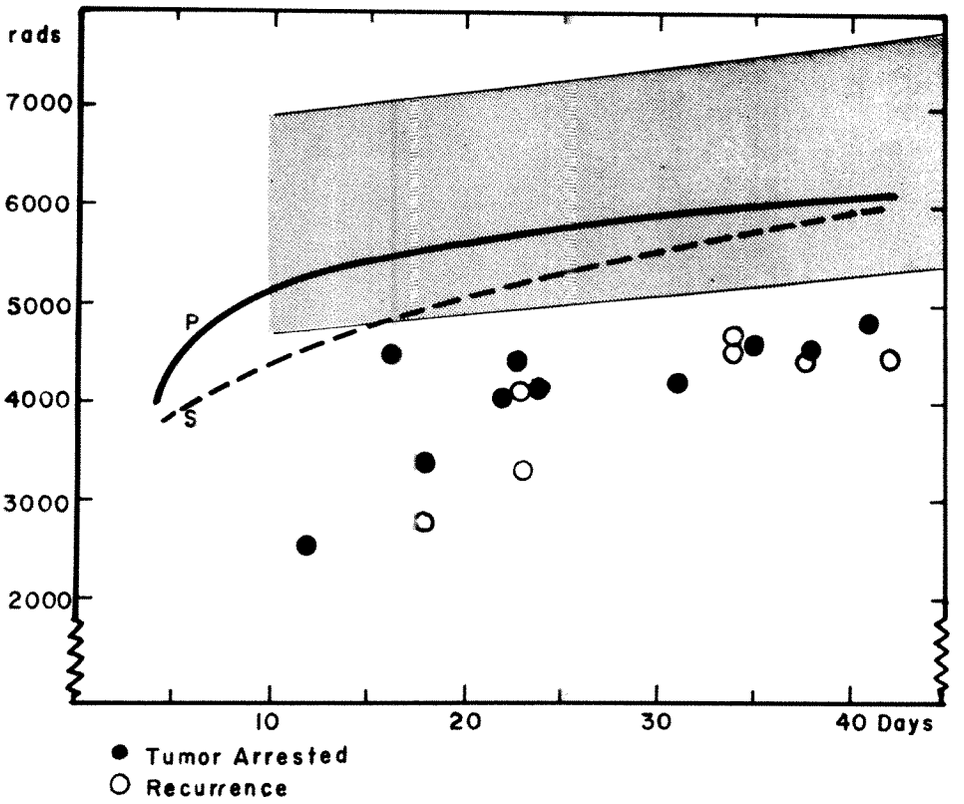


FIG. 13. Sublethal x-ray doses given to 17 lesions. Solid dots are doses which arrested the tumor for more than 1 year; circles are doses, following which, the tumor recurred. These are compared with lethal dose ranges published by Paterson (P), Strandqvist (S), and Friedman and Davis (shaded area). Ten of the 17 lesions which received methotrexate plus sublethal doses of x-rays were arrested and the patients were free of disease for more than 1 year. These data constitute the chief evidence that methotrexate can enhance radiation effects.

cases with this type of comparative study to warrant statistical analysis.

3. The third type of evidence is based on comparison of arrests of *advanced* cancer patients on a combined therapeutic regimen with previous results using radiation therapy alone. This type of comparison has weaknesses, but the improved arrest rate is so definite that it cannot be ignored. This will be shown later (Fig. 20 and 21).

CHEMORESISTANCE

Chemoresistance may be thought of as the ability of some cancer cells to adapt to the presence of an antimetabolite and survive. It is well illustrated by serial biopsy studies in Case IV. The biopsy specimen of this faucial arch carcinoma before treatment contained 2 types of cells (Fig. 14). Most of the tumor was composed of highly undifferentiated, pale-staining cells, among which were some superficially situated deep-staining cells. A dose of 95 mg. oral methotrexate was given in 11 days. On Day 29, when the tumor had shrunk 75 per cent in volume, a biopsy specimen (Fig. 15 and 16) showed that 50 per cent of the cells had been destroyed. However, the remaining cells had matured; they were more differentiated, more keratinized and exhibited no apparent destructive effects from methotrexate.[5] These were *chemoresistant* and subsequently had to be destroyed with the same large dose of interstitial irradiation, as if there had been no prior chemotherapy contribution.

On the other hand, the tumor in Case V was *chemosensitive* (Fig. 17). A dose of

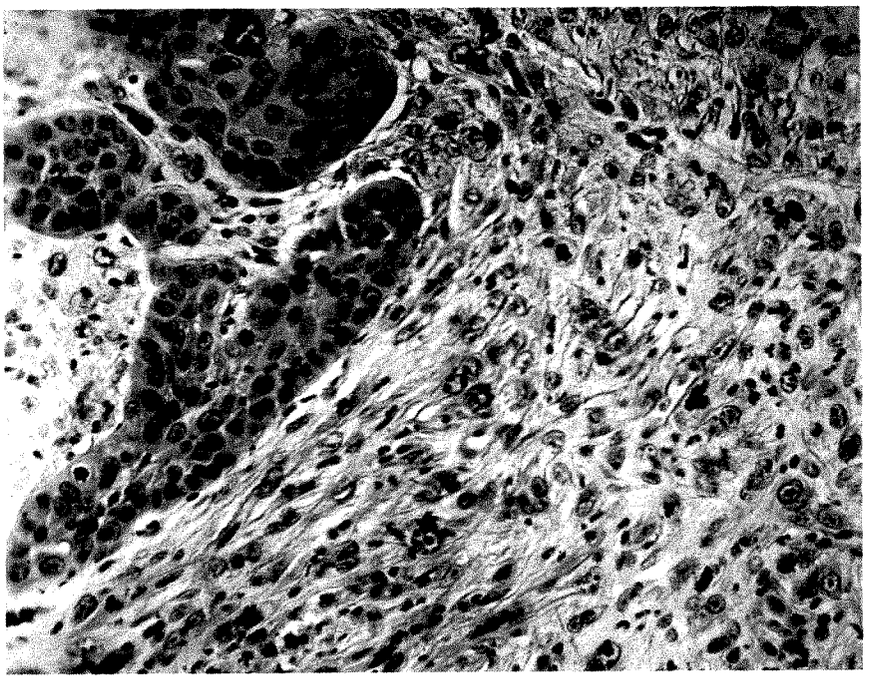


FIG. 14. Case IV. Undifferentiated squamous cell carcinoma of the faucial arch. Biopsy before treatment. Two types of cells. Most of the tumor contained undifferentiated, pale cells seen on the right half of the illustration. There were a few superficial islands of deeper-staining cells, seen on the left.

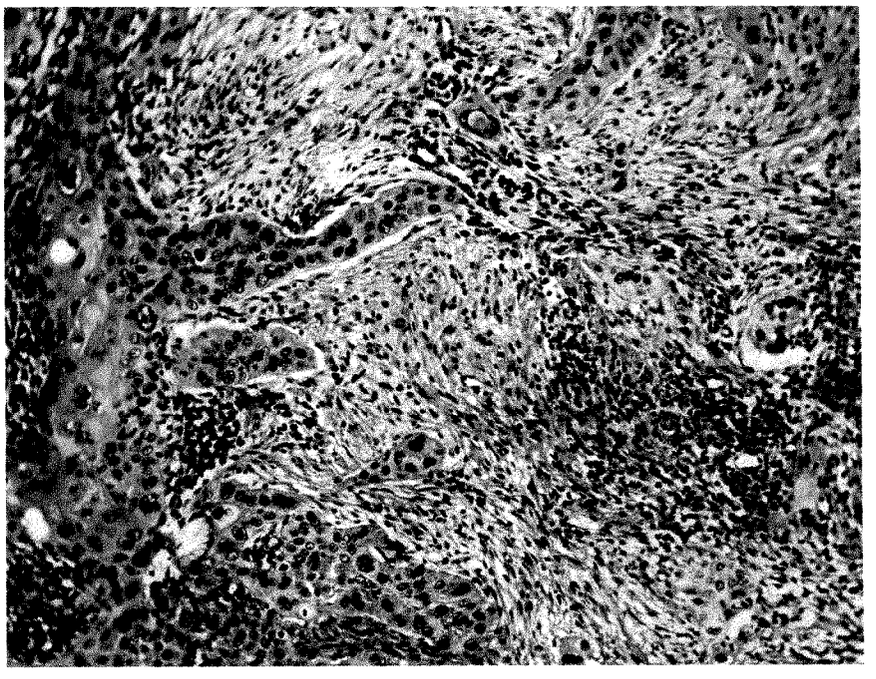


FIG. 15. Case IV. Biopsy was taken on Day 29. The tumor had shrunk 75 per cent in volume from 95 mg. methotrexate in 11 days. Low power view showing that 50 per cent of the cells were destroyed, but the remaining *chemoresistant* cells had become more differentiated and keratinized.

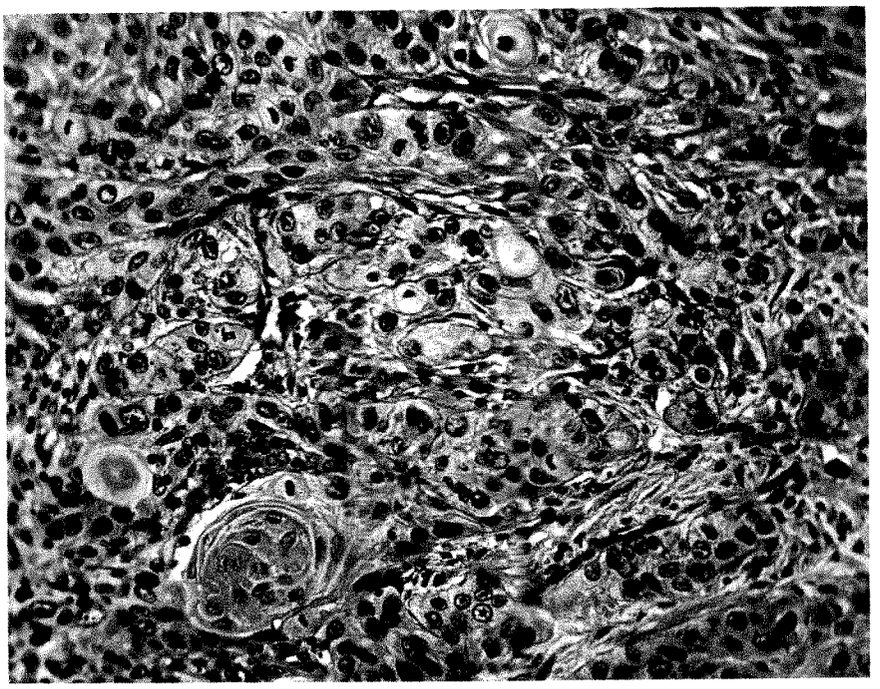


Fig. 16. Case IV. Another area of biopsy specimen removed on Day 29, and similar to Figure 15. Note the unaffected tumor cells and many residual mitoses. These *chemoresistant* cells, whose reproductive integrity is intact, recur within 1 or several months. To destroy them with irradiation, the same full lethal tumor dose is required as though there had been no chemotherapy effect.

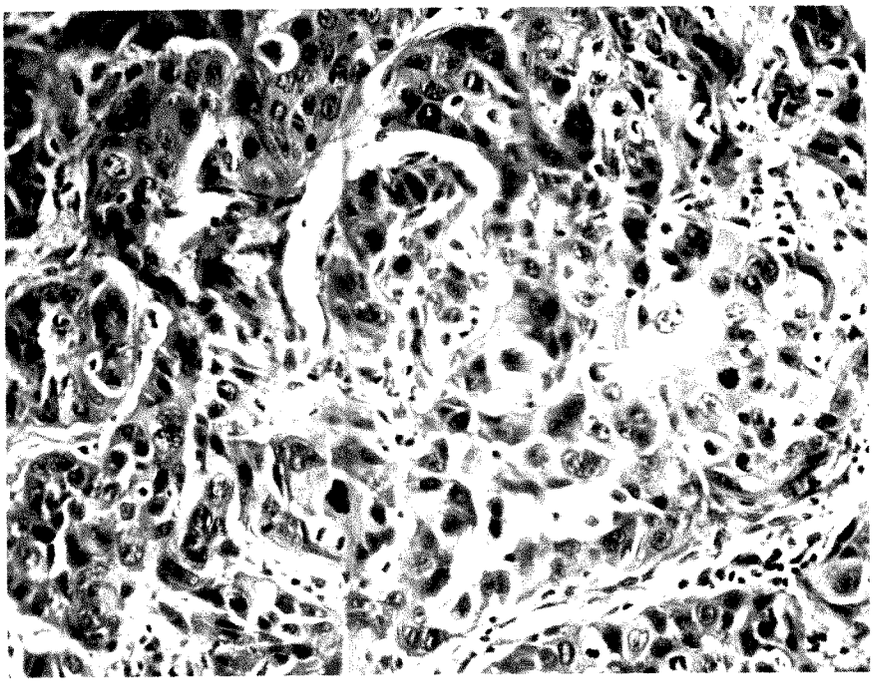


Fig. 17. Case V. Squamous cell carcinoma, Grade 3, of the posterior wall of the oropharynx. Before treatment.

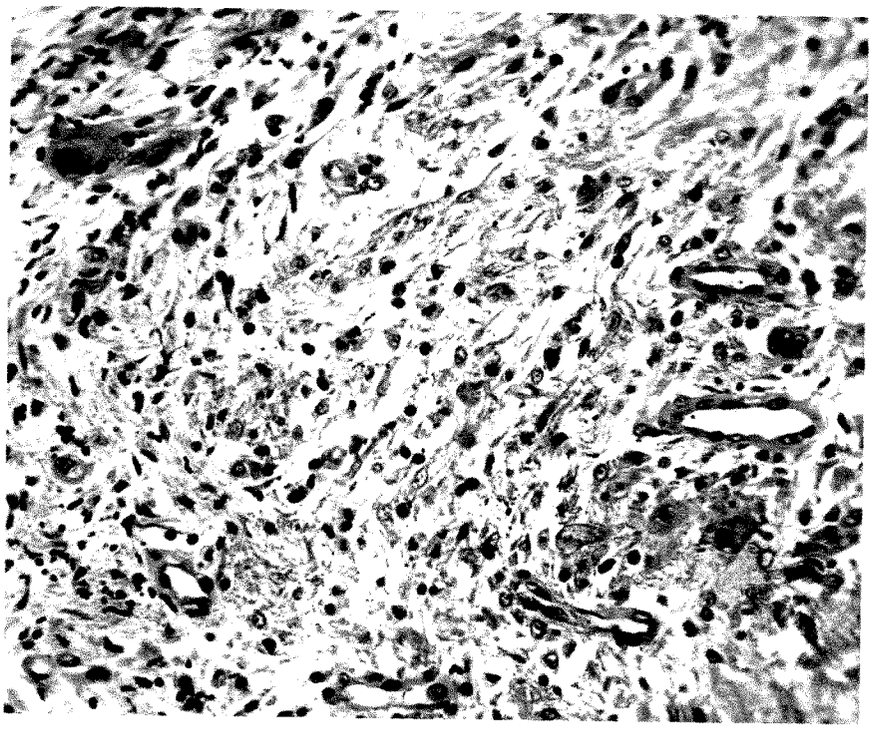


FIG. 18. Case v. Biopsy specimen taken on Day 15, one day after a total of 100 mg. oral methotrexate in 14 days. The tumor shrank 90 per cent in volume. More than 90 per cent of the cells had disappeared. Most of the tissue consisting of tumor stroma, as illustrated above, with a rare tumor cell (lower right) in advanced stage of disintegration (See Fig. 19).

100 mg. oral methotrexate was given in 14 days. On Day 15 when the tumor shrank 90 per cent in volume, a biopsy specimen now showed that 90 per cent of the cells had disappeared (Fig. 18). Only a few islands of tumor cells remained, and all of these cells showed some injury, chiefly in the form of cytoplasmic swelling (Fig. 19). There were no intact tumor cells. Thus when all the tumor cells are affected by methotrexate, however slightly, there is a probability of more efficient destruction of the tumor with combined therapy.

As stated previously, chemoresistance is the crux of the problem in combined therapy. Three patterns emerge:

1. *When all the cells are chemoresistant*, the drug produces little or no shrinkage. A full radiation dose must be given. Cure of the tumor is somewhat endangered because some normal tissues will be affected both by the drug and the irradiation, and may sustain severe reactions. In the latter event, the radiation dose may have to be curtailed or else there is an increased incidence of radiation sequelae.
2. When most of the tumor is chemosensitive and *only a few cells are chemoresistant*, the latter cells require the same tumor lethal radiation dose as though there had been no chemotherapy. There may be a more intense local reaction, but at the same time there may be an increased cure rate from combined therapy.
3. When *none of the cells is chemoresistant* and the drug affects all the cells, if only slightly, there is a real chance for increased cure rates when radiation is added.

Methotrexate makes 2 contributions toward cure. It shrinks the tumor in volume by destroying cells and it injures the remaining cells. The latter effect is more important; for, regardless of shrinkage in the

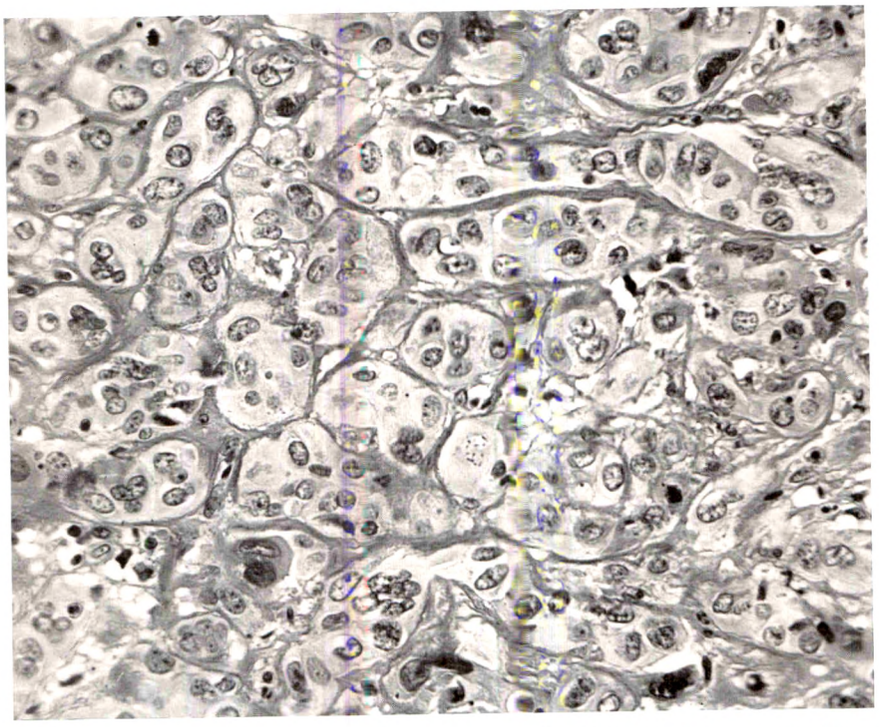


Fig. 19. Case v. Same section as in Figure 18. There is one residual island of tumor cells. However, none of the cells is intact. The ones illustrated above show some chemotherapy effect in the form of cytoplasmic swelling. Even had there been only a little shrinkage of the tumor volume and if all the cells had shown slight changes, as illustrated above, one would have expected enhanced destruction of the tumor with combined therapy.

volume of the tumor, if the remaining cells retain their reproductive integrity, the tumor will rapidly recur unless it is given a full dose of radiation just as though there had been no methotrexate effect.

Based on these observations, it is our opinion that methotrexate and irradiation each have their own specific method of damaging tumor cells independently of one another. When one modality injures the cells that are not affected by the other modality, then an enhanced destruction of the tumor occurs. Methotrexate does not specifically enhance the effect of irradiation on the cells.

EARLY RESULTS

Analysis of local control for a period of 1 year of 65 cases from University Hospital discloses some useful information (Fig. 20). Under the category T-O, are 4 cases in which the primary tumor had been surgically removed, but subsequently metastatic cervical lymph nodes appeared. The T-N categories have been grouped into 4 stages.[2] Note that in Stage II, there are 9 successes in 17 cases (53 per cent). In Stage III, there are 88 per cent successes; in the T_4 No box alone, where radiation arrests are not common, there are 7 successes among 8 cases. Finally, note that in Stage IV there are 10 out of 22 (45 per cent) 1 year local controls using combined therapy; this is much higher than with radiation therapy alone.

Not included in this diagram are 34 cases from Bellevue Hospital, a large city hospital for indigent patients. They were alcoholic, cirrhotic, undernourished, and derelict; many were over 75 years old and had marked cardiovascular-renal disease. They tolerated radiation poorly and chemotherapy less well. In this group of 34 cases there were only 3 with local control for 1

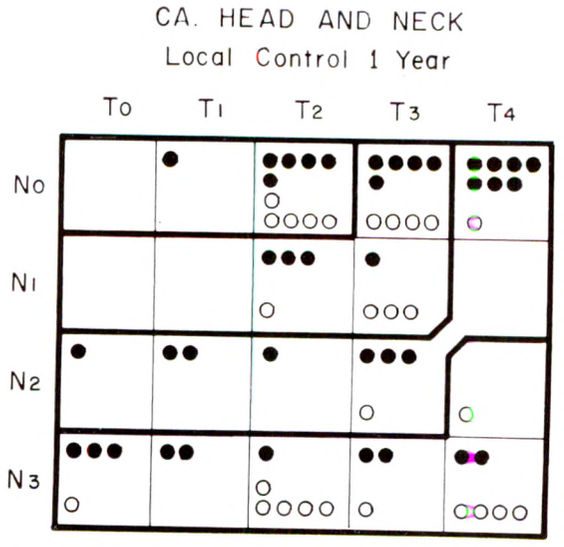


FIG. 20. One year local control in 65 cases. Note 88 per cent success in Stage III; 7 successes in 8 cases of T4 No, which is unusual; and 45 per cent successes in Stage IV.

year and only 1 patient with local control for more than 2 years. This type of patient constitutes a poor sample for this study. Chemotherapy should generally not be used for patients in poor condition of health.

Of greater significance is a group of 46 patients from University Hospital at risk for more than 2 years (Fig. 21). The 2 year arrest rate for each stage and for the whole group is about 40 per cent. A truly representative sample, having a proper distribution of cases in each stage, should yield graded results from Stage I to IV. This sample fails to do so. However, note the category T4 No, where irradiation arrests rarely occur. There are 3 tumor arrests and 3 deaths, and in 2 of the deaths there was local control of the irradiated tumor. Note Stage IV, where tumors are rarely arrested. Six lesions were arrested for more than 2 years. Of the 10 deaths, 6 tumors and their respective lymph nodes were controlled for more than 2 years, death being due to other causes or remote metastasis. It is rather unlikely that irradiation alone could achieve these results.

These results, *i.e.*, local control for 1 year (Fig. 20) and 2 year arrests (Fig. 21), are better than those previously achieved by the authors, and this evidence, although it has the weakness of any comparison with retrospective results, constitutes the hard core of evidence suggesting that combined therapy is more effective than irradiation alone.

CONCLUSIONS

1. Methotrexate, administered orally, is a useful agent when combined with irradiation for the treatment of squamous cell carcinoma of the head and neck.

2. The reported superior effect of the drug, when given by regional intra-arterial infusion, is offset by the high morbidity rate of that technique.

3. Methotrexate and irradiation each have their own specific method of damaging

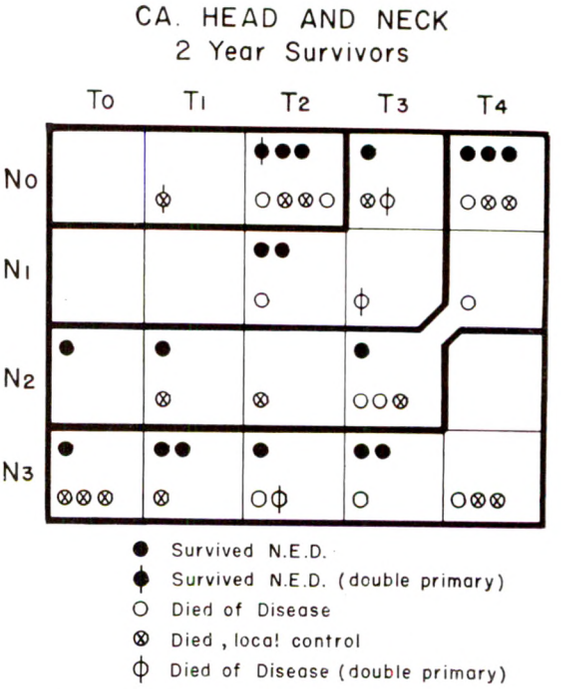


FIG. 21. Two year arrests in a series of 46 cases at risk. In the box T4 No, there are 3 arrests and 3 deaths, but in 2 patients who died, the irradiated primary tumor was arrested. These results in advanced cancer are rather unusual. It is unlikely that radiation therapy alone could achieve these results.

cancer cells and each acts independently on the tumor.

4. When combined for therapeutic purposes, the results to date suggest that the cure rates for advanced T_4 No and Stage IV squamous cell cancer of the head and neck are improved.

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CARCINOMA OF THE FLOOR OF THE MOUTH*

REVIEW OF CLINICAL FACTORS AND RESULTS OF TREATMENT

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SAN JUAN, PUERTO RICO

THE floor of the mouth is a relatively small, crescent shaped, mucosally covered area bounded anteriorly and laterally by the mandible, and posteriorly and medially by the root of the tongue, forming two sharp bilateral sulci posterolaterally at the level of the anterior tonsillar pillars. It is a readily accessible structure within the oral cavity both to inspection and palpation by the individual himself, or by the physician or dentist whom the patient might consult. It seems reasonable, therefore, to expect that malignant neoplasms in this location should be diagnosed early and if adequately treated, should have a good prognosis. Unfortunately, this is still not the general rule. The formidable problems frequently encountered in the management of carcinoma of the floor of the mouth appear disproportionately large when one considers this anatomic structure in the light of its small size, and readily accessible location. Although some authors report excellent results with moderately conservative surgical procedures[1,9] or with localized curietherapy,[3,4,9–11] these procedures yield good results only in the more localized tumors and even these are often not controlled due to the aggressive behavior of some malignant neoplasms of this location. The frequency with which carcinomas of the floor of the mouth have been found in our institution stimulated the present study, which consists of an analysis of the experience with this disease at the I. González Martínez Oncologic Hospital in San Juan, Puerto Rico. Emphasis is given to the problems of management and treatment which have been encountered.

CLINICAL MATERIAL AND INCIDENCE

Our series includes all cases with carcinoma of the floor of the mouth seen in our institution in the period between January, 1940 and December, 1965, inclusive. A total of 157 such patients was seen in this interval. At the I. González Martínez Oncologic Hospital, the floor of the mouth is the second most frequent site of cancer of the oral cavity (including lip), after cancer of the tongue. This is in agreement with the figures reported by the Puerto Rico Central Cancer Registry (Table I).

The sex distribution incidence in our series was 121 males and 36 females, a male to female ratio of approximately 3.4 to 1. Table II shows the age distribution for both sexes. The highest frequency was noted during the 5th decade for males and during the 6th decade for females. Our youngest patient was a 19 year old female and the oldest patient was 90 years old.

ETIOLOGIC FACTORS

The majority of patients with oral cavity cancer who are seen at the I. González Martínez Oncologic Hospital are from the lower socioeconomic levels, and combined conditions of poor oral hygiene, as well as deficient diets are commonly present. In addition, the widespread use of tobacco and alcohol (on many occasions "moonshine" rum), is frequently observed in our group of patients. A prior history of syphilis or the presence of leukoplakia was also found, but not as frequently as the other irritant factors. Table III presents the incidence of etiologic factors recorded and their percentage frequency. Unfortunately, as is fre-

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TABLE I

CARCINOMA OF THE FLOOR OF THE MOUTH
INCIDENCE IN PUERTO RICO*

Years	Floor of Mouth†		Tongue		Other Oral Cavity Sites‡	
	Male	Female	Male	Female	Male	Female
1950–1961	1.4	0.5	3.9	1.4	2.3	1.5
1962	2.9	0.9	5.3	1.4	3.3	0.6
1963	1.1	0.5	5.3	1.8	5.3	1.8
1964	2.0	0.8	5.4	1.2	4.3	1.5

* Crude incidence rates per 100,000 population. Data from Puerto Rico Central Cancer Registry.
† Includes lower gum.
‡ Includes buccal mucosa, upper gum, palate, and oral cavity not otherwise specified.

quently the case in a retrospective analysis, it was not possible to estimate the quantity or intensity of use of irritants of probable etiologic importance such as tobacco and alcohol.

PATHOLOGY

The great majority of the cases included in our series (96.2 per cent) had the diagnosis confirmed histologically. The 6 cases which were not confirmed histologically but were included in our series all died with clinical evidence of carcinoma of the mouth within 12 months after diagnosis. The histologic diagnosis of epidermoid carcinoma was made in all cases except 1 which was mucoepidermoid carcinoma. In 1 of the histologic specimens, there was marked eosinophilic infiltration and in another there were pseudosarcomatous areas within the epidermoid carcinoma. All of the available slides were recently reviewed by a member of our pathology department, and out of 110 specimens which were thus reexamined, the initial diagnosis was reconfirmed in all cases.

EXTENT OF PRIMARY TUMOR

The extent of the primary lesions is shown in Table IV. Of the total series, 65 patients (41.4 per cent) had tumors localized to the floor of the mouth; 41 patients (26.1 per cent) had invasion of the tongue, and 10 (6.4 per cent) had anterior extension to the gum (with or without clinical invasion of the mandible). Extension of the tumor to both the tongue (medially or posteriorly) and the gum (anteriorly or laterally) was present in 18 patients (11.5 per cent), while extension out of the oral cavity (subcutaneous submental tissue or skin), or posteriorly into the oropharynx was encountered in 16 patients (10.1 per cent). The information available was insufficient to determine extent in 7 cases.

METASTASES

Palpable lymph nodes clinically representing metastases were present in 100 cases (63.7 per cent) at the time of admission; of these 30 (30.0 per cent) were confirmed by histopathology. Most of these were confirmed by open biopsy or by radical neck dissection. However, confirmation by

TABLE II

CARCINOMA OF THE FLOOR OF THE MOUTH
AGE AND SEX DISTRIBUTION

Age Range (yr.)	No. of Patients		
	Male	Female	Total
10–19	0	1	1
20–29	0	0	0
30–39	2	0	2
40–49	19	4	23
50–59	46	5	51
60–69	26	12	38
70–79	24	9	33
80–89	3	3	6
90–99	1	2	3
	121	36	157

TABLE III

CARCINOMA OF THE FLOOR OF THE MOUTH
FREQUENCY OF ETIOLOGIC FACTORS
INCIDENCE AND PER CENT FREQUENCY BY SEX

	Not Stated		Yes		No	
	Male	Female	Male	Female	Male	Female
Tobacco	18 (15%)	5 (14%)	102 (84%)	26 (70%)	1 (1%)	5 (14%)
Alcohol	40 (33%)	13 (35%)	62 (51%)	7 (19%)	19 (16%)	16 (43%)
Poor oral hygiene (poor teeth)	39 (32%)	12 (33%)	70 (58%)	21 (57%)	12 (10%)	3 (8%)
Leukoplakia	53 (44%)	21 (58%)	14 (12%)	2 (5%)	54 (45%)	13 (35%)
Lues	24 (20%)	11 (30%)	23 (19%)	2 (5%)	74 (61%)	23 (64%)

Total No. of Cases:
Male 121
Female 36

needle biopsy during the course of radiotherapy (usually after 1,000 r had been delivered) was obtained in some instances where large lymph nodes were present. During the early part of the period included in this report treatment of enlarged lymph nodes without attempts to obtain biopsy was common; however, our present policy is to obtain histologic confirmation with needle biopsy whenever possible. Ten patients developed lymph node metastases subsequently during their course; thus the total incidence of lymph node metastases during the course of the disease was 110 cases (70.1 per cent). No distant metastases were initially found at the time of diagnosis; however, 6 patients developed distant metastases during the course of their disease. Five of these had epidermoid carcinomas, while 1 lacked histologic confirmation of the primary tumor.

TABLE IV

CARCINOMA OF THE FLOOR OF THE MOUTH
ANATOMIC EXTENSION OF PRIMARY TUMOR

Localized to floor of mouth	65 (41.4%)
Invasion of tongue	41 (26.1%)
Invasion of gingiva and/or mandible	10 (6.4%)
Invasion of tongue and gingiva and/or mandible	18 (11.5%)
Anterior extension out of oral cavity (skin or submental subcutaneous tissues)	12 (7.6%)
Posterior extension out of oral cavity into oropharynx	4 (2.5%)
Extent not known	7 (4.5%)
	157

PRESENCE OF OTHER CANCER

The presence of other primary cancers in our series, excluding skin, was established in 16 patients (10 per cent), and is shown in Table v. Of these, 2 preceded the presence of carcinoma of the floor of the mouth, 5 were discovered concurrent with it and 9 became manifest after this lesion had been treated. The most frequent site found for the other cancer was palate (5

TABLE V

CARCINOMA OF THE FLOOR OF THE MOUTH
PRESENCE OF OTHER CANCERS*
TIME OF MANIFESTATION RELATIVE TO DIAGNOSIS
OF CARCINOMA OF FLOOR OF MOUTH

	Before	Concurrent	After	Total
Palate	1	1	3	5
Tonsil	1	—	2	3
Base of tongue	—	1	1	2
Vallecula	—	1	—	1
Hypopharynx	—	—	1	1
Esophagus	—	2	1	3
Stomach	—	—	1	1
	2	5	9	16

* Excluding cancer of skin.

Table VI

CARCINOMA OF THE FLOOR OF THE MOUTH
EXTENT OF DISEASE (TNM)

	T_1	T_2	T_3	T_4	Unclassified	Total
N_0	26	15	13	0	2	56 (35.7%)
N_1	8	16	15	8		47 (29.9%)
N_2	1	8	20	8		37 (23.6%)
N_3	0	2	10	2		14 (8.9%)
Unclassified					3*	3 (1.9%)
Total	35 (22.3%)	41 (26.1%)	58 (36.9%)	18 (11.5%)	5 (3.2%)	157

* Two cases with neck metastases not classifiable. No cases found with distant metastases at time of initial diagnosis.

cases), followed by esophagus (3), tonsil (3), base of tongue (2), and other sites in the upper alimentary tract including 1 case of carcinoma of the stomach.

CLASSIFICATION AND STAGING OF TUMOR EXTENT

The cases were classified according to a modification of the TNM system as proposed by the Committee on Radiation Therapy Studies (CRTS). T_1 lesions were 2 cm. or smaller in size, T_2 tumors were greater than 2 cm. and up to 4 cm., with or without limited mucosal extension to tongue or gingiva. T_3 lesions were those greater than 4 cm. in size, with frank invasion of tongue and/or gingiva, and T_4 tumors were massive lesions which extended posteriorly out of the oral cavity into the oropharynx or anteriorly out of the mouth (skin or massive subcutaneous submental infiltration), or had frank destruction of mandible. The N_0 group had no palpable lymph nodes; N_1 consisted of cases with movable unilateral lymph nodes; N_2 cases had bilateral movable lymph nodes or single fixed lymph nodes of 3 cm. or less in greatest dimension; and N_4 included cases with a single fixed lymph node larger than 3 cm. or multiple fixed lymph nodes. No patient had distant metastases manifested before treatment in our series. Table VI shows the distribution of our material according to the TNM classification.

For the purpose of analyzing results, we have also grouped the cases into Stages I through IV based on the TNM classification (Table VII). This staging is arbitrary but is simple and thought to be reasonable in the light of the survival results obtained. The largest number fell in the Stage III group (57 cases); with Stage I having 26 cases; Stage II, 39 cases; and Stage IV, 30 cases, respectively. Five cases could not be staged because of insufficient information.

TREATMENT

Table VIII shows the distribution of cases as to treatment modality employed during 2 periods of time (1940–1955 and 1955–1965). A number of cases (19 per cent in 1940–1955 and 7 per cent in 1955–1965) was not treated for a variety of reasons; some came for consultation only, some refused treatment and others were too far advanced for therapy. During both periods, radiation therapy has been the preferred modality of treatment for these cases.

In October, 1955 one of us (V.M.) took charge of providing radiation therapy services at our institution; since then, the following philosophy of treatment has prevailed: When possible, carcinomas of the floor of the mouth with well delimited borders measuring less than 2 cm. in size are submitted to interstitial implantation; exception to this are cases with invasion of the gingiva. Lesions with ill defined borders or when 2 cm. or larger or with gingival ex-

TABLE VII

CARCINOMA OF THE FLOOR OF THE MOUTH
STAGE OF DISEASE

	T_1	T_2	T_3	T_4
N_0	Stage I 26 (16.6%)			
N_1		Stage II 39 (24.8%)		
N_2			Stage III 57 (36.3%)	
N_3				Stage IV 30 (19.1%)

TABLE VIII

CARCINOMA OF THE FLOOR OF THE MOUTH
TREATMENT DISTRIBUTION

	January 1940 to October 1955		October 1955 to December 1965	
Not treated at I. González Martínez Oncologic Hospital	11	19%	7	7%
Roentgen therapy alone	28	47%	5	5%
Cobalt 60 teletherapy alone	0		35	35%
Interstitial implantation alone	0		4	4%
Surgery alone	9	15%	6	6%
Roentgen and/or Co^{60} therapy and interstitial implantation	7	12%	37	37%
External irradiation or interstitial implantation followed by surgery	0		3	3%
Surgery followed by radiotherapy	2	4%	0	
Electrocoagulation followed by radiotherapy	2	4%	0	
Chemotherapy plus radiotherapy	0		1	1%
Total	59	100%	98	100%

tension require external irradiation prior to interstitial curietherapy. Extensive bulky tumors are usually treated with external irradiation alone; however, if during or after this therapy the size of the neoplasm is significantly reduced, an implantation may be done. Cases with frank bone invasion are best handled by surgery with or without preoperative irradiation. The presence of palpable lymph nodes in the neck is not a contraindication to radiation therapy of the primary lesion. The lymph nodes may be included in the field of irradiation and surgery can be practiced for the neck problem after the primary lesion has been treated with irradiation. Since the availability of cobalt 60 teletherapy (November, 1956), tumors requiring external irradiation alone have received exposures of 6,000 r in 7 weeks. However, peroral irradiation has been administered with orthovoltage equipment. For interstitial curietherapy, we have employed low intensity radium and cobalt 60 needles in all but 6 cases which were implanted with iridium 192 wire in nylon ribbons. When interstitial curietherapy is the only treatment, the tumor doses range from 6,000 to 7,000 r in 5 to 7 days; however, when treated first by external irradiation, this latter technique contributes a dose ranging from 3,000 to 5,000 r in 3 to 6 weeks and the implant dose is reduced proportionately.

COMPLICATIONS

The most frequent treatment complication encountered was radionecrosis of soft tissues and/or bone which occurred in 19 patients (15 per cent of the 124 treated with some form of radiotherapy in our institution). Of these, bone exposures occurred in 12 patients. Eight of these patients had no recurrence of primary tumor and 1 had a recurrence $3\frac{1}{2}$ years after the onset of radionecrosis with bone exposure. In the remaining 3 patients bone exposures were felt to have occurred as a result of radionecrosis of overlying soft tissue, but recurrent disease was found to be also present. Necrotic ulcerations of soft tissues alone, without bone exposures, occurred concurrently with recurrence of neoplasm in 3 cases and in the absence of recurrence in 4 cases. One of the latter was found to have roentgenographic evidence of necrosis of the mandible subsequent to healing of the soft tissue necrotic ulcer but has never developed bone exposure. Other complications which occurred were operative or postoperative deaths (4 cases), postoperative wound infection (2 cases), and salivary fistula in 1 case.

Table IX

CARCINOMA OF THE FLOOR OF THE MOUTH
SURVIVAL BY STAGE

Stage	No. of Patients	Per Cent 3 Year Survival	Per Cent 5 Year Survival
I	26	78.3%	68.5%
II	39	39.3%	28.6%
III	57	29.0%	22.4%
IV	30	12.4%	7.4%
Unclassified	5	20.4%	0.0%
	157	36.3%	28.1%

TREATMENT RESULTS

The 5 year survival rate of our series was calculated by the actuarial method. The over-all 5 year survival of the entire series was 28.1 per cent $\pm$ 4.0 per cent. The 5 year survival calculated by the direct method was almost identical. Twenty-eight out of a total of 102 patients eligible for 5 year analysis survived 5 or more years for a figure of 27.4 per cent. Three cases were lost to follow-up before 5 years. If we exclude those patients that were not treated at our institution (either because they were treated at other institutions, refused treatment, or were too advanced to be acceptable for treatment other than analgesic medication), the 5 year survival of the remaining group (139 patients, calculated by the actuarial method) was 30.6 per cent $\pm$ 4.4 per cent.

The 5 year survival related to stage of disease is shown in Table IX. Patients with

TABLE X

CARCINOMA OF THE FLOOR OF THE MOUTH
SURVIVAL BY TREATMENT

Treatment	No of Patients	Per Cent 3 Year Survival	Per Cent 5 Year Survival
Not treated at I. González Martínez Oncologic Hospital	18	15.8%	10.5%
Roentgen therapy alone	33	35.1%	31.2%
Cobalt 60 teletherapy alone	35	20.9%	0.0%
Surgery alone	15	14.3%	7.1%
Roentgen and/or cobalt 60 therapy and interstitial implantation	44	58.6%	45.2%
Interstitial implantation alone	4	—	—*[1]
Radiotherapy plus surgery	3	—	—*[2]
Surgery followed by radiotherapy	2	—	—*[3]
Electrocoagulation followed by radiotherapy	2	—	—*[4]
Chemotherapy plus radiotherapy	1	—	—*[5]
	157	36.3%	28.1%

* Number of cases too small for survival determination by actuarial method.
[1] Three cases (75%) controlled for 5 years or more.
[2] One case (33%) controlled for 4½ years; no evidence of disease at last follow-up.
[3] One case (50%) controlled for more than 5 years.
[4] One case (50%) controlled for more than 5 years.
[5] Palliative treatment, alive with disease at 6 months.

Stage I lesions (2 cm. or less, limited to the floor of the mouth and without metastases) had the best results. Those with larger lesions with invasion of adjacent structures and/or the presence of lymph node metastases had poorer 5 year survival.

Table X shows the 3 and 5 year survival according to the type of treatment. Roentgen therapy alone (external and peroral cone) gave a 31.2 per cent 5 year survival rate. The best survival by treatment was noted in patients with either external roentgen therapy or cobalt 60 teletherapy plus interstitial implant (45.2 per cent). An interstitial implantation alone was feasible in 4 patients, of whom 3 survived free of disease for more than 5 years. The 5 year survival rate for Co^{60} teletherapy alone as the primary treatment was 0.0 per cent; of the 35 patients thus treated, 14 were in Stage IV, 15 in Stage III, 5 in Stage II, and 1 in Stage I. Of these, only 3 (2 Stage II and 1 Stage III) are living without evidence of disease for more than 2 years, and all 3 required additional treatment (interstitial implantation in 2 cases and radical surgery plus further radiation therapy in the other) for residual or recurrent disease. The patient with Stage I disease was not controlled; this patient also had interstitial radium implantation for persistent tumor, but had a recurrence subsequently and died with disease after living more than 4 years after treatment.

Of 15 patients whose primary treatment was radical surgery, the 5 year survival was 7.1 per cent. Eight of the 15 patients thus treated had Stage III lesions, of which none survived 5 years, 5 had Stage II lesions with none surviving, and 2 had Stage I lesions of which one remained controlled for more than 5 years.

DISCUSSION

Althouth the incidence of cancer of the floor of the mouth has been found to be low by some authors,[2,11,15] we have found it to be the second most frequent site of cancer of the oral cavity, second only to cancer of the tongue. A high incidence has also been reported by other authors[14] and it is probable that there exist similarities in the types of populations which they studied with our clinical material regarding possible etio-

logic factors such as dietary deficiencies, poor oral hygiene, and the prevalent use of irritants such as tobacco and/or alcohol. The relative sex incidence reported by various authors[1–5,8,12,14,15] ranges from a male to female ratio of 49 to 1[12] to 2 to 1.[2] The male to female incidence ratio of 3.4 to 1 that we encountered in our series falls within the reported extreme values but close to the lower value. We disagree with the implication[8] that a high female incidence of cancer of the floor of the mouth implies incorrect site diagnosis with resulting inclusion of lesions of the tongue as primary neoplasms in the former location. All of the head and neck cancer patients seen in our institution are initially evaluated by an otorhinolaryngologist after which the patient is seen by other staff members in a joint conference in order to decide on the type of treatment; therefore, we feel confident that a possible error due to incorrect classification of primary site in our present series is unlikely.

The incidence of regional lymph node metastases which we found (70.1 per cent) is higher than the figures given by other authors[4,5,8,12] reporting large series. Distant metastases from carcinoma of the floor of the mouth have been described to be frequent, compared with other oral cavity sites.[7] In our material 6 patients had distant metastases during the course of the disease. The metastatic sites were lung in 2 cases, skull and long bones in 2 cases, and subcutaneous structures (chest wall and abdominal wall) in 2 cases. The time interval between diagnosis and manifestation of the distant metastases was 6 months to 2 years.

The preferred method of treatment in our series has been radiotherapy. Small, well circumscribed lesions have responded well to interstitial implantation alone, while larger lesions have been treated primarily with a combination of external irradiation followed by interstitial implantation for the residual tumor. Although some cases have been initially treated by surgery alone in the past, the results have not been adequate. If a lesion is small enough to be treated by wide excision alone, we have found interstitial curietherapy alone, or preceded by a short course of external irradiation, to be a preferred procedure, as the final results are as good as those after surgery. However, one occasionally encounters small lesions that do not respond well to radiotherapy; therefore, we feel that a close follow-up evaluation of the patient is imperative and that surgical intervention should not be delayed if the initial response to radiotherapy is incomplete. Patients with large tumors in which one anticipates poor results with either radiotherapy or surgery alone should be considered candidates for a combination of radiotherapy followed by surgery from the start, and thus some patients with apparently hopelessly advanced tumors can occasionally be salvaged by such a combined approach. We have preferred radical neck dissections for the treatment of metastatic lymph nodes if the surgical criteria have been met and the primary tumor has been under control. We agree with others[6] that radical neck dissection is a safe procedure in spite of previous intensive irradiation and may considerably improve the end results in the treatment of the neck metastases. Large inoperable lymph nodes which have persisted after external irradiation have occasionally been controlled by further external irradiation with limited tangential fields, or by interstitial radioisotope implantation provided that the primary tumor was controlled.

The use of iridium 192 in nylon ribbon has added more flexibility in the execution of interstitial implantation. It has proved useful in allowing better distribution of the radioactive sources while being able to conform to the anatomic configuration of the volume implanted than with rigid needles of fixed lengths. In addition, the advantages of lower energy gamma emission (0.30 mev.–0.61 mev.) and the afterloading techniques, to which iridium ribbon is ideally suited, decrease the radiation exposure hazards to the patient and the operating personnel, while allowing fluoroscopic confir-

TABLE XI

CARCINOMA OF THE FLOOR OF THE MOUTH
TYPE OF PRIMARY TREATMENT AND STAGE OF DISEASE

Treatment	Stage I	Stage II	Stage III	Stage IV	Unclassified	Total
Not treated at I. González Martínez Oncologic Hospital	3	1	4	8	2	18 (11.5%)
Roentgen therapy alone	6	11	9	4	3	33 (21.0%)
Cobalt 60 teletherapy alone	1	5	15	14	—	35 (22.3%)
Surgery alone	2	5	8	—	—	15 (9.6%)
Roentgen and/or cobalt 60 therapy and interstitial implantation	9	14	19	2	—	44 (28.0%)
Interstitial implantation alone	3	1	—	—	—	4 (2.5%)
Radiotherapy plus surgery	—	1	1	1	—	3 (1.9%)
Surgery followed by radiotherapy	—	1	1	—	—	2 (1.3%)
Electrocoagulation followed by radiotherapy	2	—	—	—	—	2 (1.3%)
Chemotherapy plus radiotherapy	—	—	—	1	—	1 (0.6%)
	26 (16.6%)	39 (24.8%)	57 (36.3%)	30 (19.1%)	5 (3.2%)	157

mation of the implant arrangement prior to insertion of the isotope. Among the disadvantages, including economics, have been the short half life of Ir^{192} (74.4 days) and the relative difficulties in calculating accurate dose distributions of the implanted volume.

We have used iridium 192 for implantation in 6 patients, usually for the more advanced lesions after external radiotherapy has decreased the size of the primary tumor. However, 1 patient was treated by iridium implantation alone for an early (T_1N_0) lesion with excellent results. Of the remaining 5 patients, 1 had a T_4 tumor which was not controlled and the other 4 had T_3 lesions of which 2 were controlled for $4\frac{1}{2}$ and 5 years. All of these 5 patients had external cobalt 60 teletherapy prior to iridium 192 interstitial implantation.

The complication which was most frequently encountered in our series was radionecrosis of soft tissues and/or bone. This complication could be correlated with a high local dose in all instances except 1. This 1 exception, however, developed osteoradionecrosis after radical surgery, complicated by infection and salivary fistula, performed because of recurrent disease after roentgen therapy. It was not possible to obtain exact information of the time interval between dental extractions and onset of radiotherapy in many instances; however, most of the patients had been without their teeth for a considerable length of time. We agree with other authors[2,8,13] who stress that the teeth in the proposed area of irradiation should be removed prior to radiotherapy. A careful alveolectomy and proper mucosal closure should be performed and irradiation started after a rest of 1 or 2 weeks. It is noteworthy that mucosal and/or bone necrosis were encountered in 3 patients who had iridium 192 implantation after external cobalt 60 teletherapy. We feel certain that this was due to the intense local dose delivered. It is also noteworthy that we have not observed any radionecrosis problems with cobalt 60 needle implants although we have been using these sources since 1959. Whether this is due to the higher energy of the gamma rays emitted with less bone absorption remains a point for further study.

The results of treatment of early lesions (Stage 1) have been satisfactory with a 68.5 per cent 5 year survival rate. The large majority of these were treated by radiotherapy. Table XI shows the distribution of stage of disease according to type of treat-

ment. It has been the opinion of several investigators[4,9,12] that radiotherapy can produce as good results as wide surgical excision advocated by some authors[1] for early lesions; therefore, surgery was not employed more often in the treatment of these lesions. More advanced primary lesions if treated by surgery would require a radical resection with at least hemimandibulectomy and we have preferred to reserve this type of procedure for those patients who have not responded to radiotherapy but are otherwise suitable candidates for surgery. Of the 15 patients treated initially by surgery alone, only 2 had Stage I disease, while 5 had Stage II disease, and 8 patients had Stage III disease. Only 1 of the Stage I cases was controlled, the others remained uncontrolled.

Surgery was employed for secondary treatment after radiotherapy in 25 cases for residual or recurrent disease. Of these, 12 had radical resections with neck dissection, 7 had radical neck dissections, 2 had suprahyoid dissections and 4 had local excisions of recurrent lesions. Eight of the 25 patients (32 per cent) who had subsequent surgery have remained free of disease for varying periods of time. Of the 12 patients who had radical resections for residual or recurrent disease, 1 lived free of disease for more than 5 years, and 2 others are alive without evidence of disease for 12 and 27 months. Two of 7 patients with radical neck dissections have no evidence of disease at 9 and 12 months and both patients who had suprahyoid neck dissections have been without evidence of disease for 2 and 17 years. One patient who had wide local excision for recurrence has no evidence of disease at 12 months. The surgical complications which have been mentioned (mortality, 4 cases; wound infection, 2 cases; and salivary fistula, 1 case) were from the total of 40 cases treated by surgery —15 as initial treatment, and 25 as secondary treatment after radiotherapy.

The present report illustrates the difficulties frequently encountered in controlling this disease except in its earliest stages. Although improvements in surgical and radiotherapy techniques may offer better results in the advanced cases, particularly utilizing combinations of treatment modalities such as chemotherapy, radiotherapy, and surgery, further efforts in the fields of prevention and early detection seem indicated. An improvement of hygienic habits and decrease in the use of irritants through education of the public seem essential. In addition, an increased awareness of the physician or dentist who might see a patient with a suspicious lesion in the oral cavity should be stressed. No lesions in the mouth should be followed with conservative measures for more than 2 weeks. If a lesion persists after this length of time in spite of conservative treatment, biopsy is mandatory. Once the diagnosis has been established, definitive treatment should not be delayed further, but it should be carefully planned. This requires close cooperation between the radiotherapist, surgeon and chemotherapist in order that all of the treatment modalities may be utilized to the fullest of their potential and provide the best opportunity for control of the disease.

SUMMARY

1. The experience at the I. González Martínez Oncologic Hospital with 157 cases of carcinoma of the floor of the mouth between the years 1940 and 1965, inclusive, is reviewed.

2. The sex incidence and etiologic factors are discussed. Carcinoma of the floor of the mouth has been the second most frequent form of cancer of the oral cavity seen in our institution.

3. The methods of treatment are discussed and the results of treatment are given in terms of 5 year survival, being 28.1 per cent for the entire series.

4. Patients with localized small lesions limited to the floor of the mouth without lymph node metastases (Stage I lesions) had the best 5 year survival rate (68.5 per cent).

5. The treatment modality which

yielded the best results was external irradiation followed by interstitial curietherapy (45.2 per cent), including lesions of all stages.

6. The most frequent complication to treatment encountered was radionecrosis of the mandible and/or soft tissues (15 per cent).

7. Six patients were treated with iridium 192 implantation; in 5 of the 6 the implantation was preceded by a course of external therapy of whom 2 were controlled and 1 patient with a small lesion was treated successfully with iridium 192 implantation alone.

8. We believe that radical surgery is best employed for the treatment of lymph node metastases and for the management of recurrent or residual primary lesions.

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CANCER OF THE NASOPHARYNX*

142 PATIENTS TREATED IN THE 11 YEAR PERIOD 1950–1960

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IN 1958 a series of 88 cases of nasopharyngeal cancer treated at this institution in the years 1945 through 1949 was reported. Since that time, considerable modification in our treatment methods has taken place. These changes comprise essentially a tendency toward the use of higher orthovolt dosage in the early 1950s, the advent of cobalt 60 teletherapy in the mid 1950s, and the introduction of split-dose methods in the late 1950s. One purpose of this paper, therefore, is to ascertain if possible what influences these changes in treatment technique have produced in the salvageability of patients with nasopharyngeal cancer and to determine if possible along what lines progress, if any, was being made.

MATERIAL AND METHOD

Data were reviewed on 142 patients with nasopharyngeal cancer who had received their primary definitive treatment at the Mayo Clinic in the years 1950 through 1960. Excluded were patients who had received their primary definitive therapy elsewhere and who were seen at the Mayo Clinic after recurrence for which either minimal additional palliative therapy was undertaken or for whom no additional therapy of any sort seemed indicated. Also excluded were patients who elected to return home for definitive therapy after the initial diagnosis of nasopharyngeal cancer had been made here.

Sex and Age Distribution. The ratio of males to females was 2.4:1 (Table I). This ratio is similar to most other reported ratios (between 2:1 and 3:1). Most patients (71 per cent), as has been reported by others, were in the fifth, sixth, and seventh decades of life. We were unable to verify the often-reported relative preponderance of this disease in Orientals; there were no Orientals in our series, undoubtedly a reflection of the midwestern location of our institution.

TABLE I

RELATION OF SEX AND AGE TO SURVIVAL

	Patients	
	No.	Survived 5 Yr. (%)
Sex		
Males	100	29
Females	42	33
Age, years		
<10	5	0
10–19	5	0
20–29	8	50
30–39	13	38
40–49	27	37
50–59	43	28
60–69	31	32
70–79	7	29
≧80	3	0
Total	142	30

Presenting Symptoms. Data on presenting symptoms are given in Table II. This rather bewildering array of complaints may explain in part some of the diagnostic errors encountered in this "blind" area of the upper respiratory tract; although nasopharyngeal cancers make up perhaps 1 to 2 per cent of all malignant tumors of the

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Mayo Clinic and Mayo Foundation: Section of Therapeutic Radiology (Dr. Scanlon), of Surgical Pathology (Dr. Woolner), of Plastic Surgery (Dr. Devine), and of Otolaryngology and Rhinology (Dr. McBean). Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Otolaryngology and Rhinology (Dr. Rhodes).

TABLE II

PRESENTING SYMPTOMS

	Patients		
	No.	% of 142	Survived <5 Yr. (%)
Cervical lymphadenopathy	60	42	76
Pain in head, neck, or face	45	32	77
Hearing loss	41	29	73
Nasal obstruction or stuffiness	40	28	72
Nasal or oral bleeding	27	19	59
Diplopia, blurred vision, or eye pain	22	15	77
Ear block or tinnitus	20	14	80
Ear pain	19	13	74
Weight loss	12	8	—

Others: facial paresthesias in 10; sore throat in 8; dysphagia in 6; anorexia in 6; nasal discharge (nonbloody) in 5; weakness and fatigue in 5; loss of taste in 4; hoarseness in 4; no symptoms (lesion accidentally found during routine examination) in 4; and speech difficulty in 3; malaise, proptosis, nasal regurgitation, chronic sinusitis, dizziness, nausea, and vomiting in 2 each; visible tumor below palate, peripheral arthritic pain, trismus, fever, insomnia, loss of smell, ear discharge, chronic rhinitis, and feeling of fullness in the throat in 1 each.

body and approximately 18 per cent of all tumors of the head and neck,[19] they remain one of the most consistently misdiagnosed of all human malignancies.

Pathologic Aspects. As stated in our previous publication, there is probably no other single regional group of cancers of the respiratory system about which there is less agreement in the world literature with regard to the correct and proper pathologic classification. In our previous review of the literature, we found that squamous cell epithelioma ranged in frequency from a high of 67.8 per cent reported by New and Stevenson[10] to a low of 6 per cent reported by Martin and Blady,[9] with intermediate frequencies varying from 20 and 45 per cent. The past decade has seen little progress in standardizing the classification of these cancers, with even greater extremes being noted in the recent literature. Thus, Schmidt[17] classified 101 of 103 cancers of the nasopharynx as squamous cell carcinomas. At the other extreme, Vaeth[19] classified 17 per cent of his 82 tumors as epidermoid carcinomas. As a further example of the futility of trying to compare pathologic classifications of nasopharyngeal cancers, at the other end of the scale, the reported incidence of lymphosarcoma ranges from our extreme low of 3.5 per cent and Vaeth's low of 4.9 per cent up to those of 20 to 40 per cent reported by Lenz,[8] Baclesse and Dulac,[2] Nielsen,[11] Martin and Blady,[9] and Eberhard and Leaming.[4]

In our series, as in a previously reported series, we subdivided nasopharyngeal cancers on a microscopic basis into 3 main groups: (1) squamous cell carcinoma, (2) undifferentiated carcinoma (lymphoepithelioma), and (3) miscellany (Table III). The first group includes only tumors that show microscopic evidence of keratinization. The second group (undifferentiated neoplasms) has contributed greatly to the difficulty of classification. Some series have attempted to subdivide the group into lymphoepithelial and transitional cell types. We doubt

TABLE III

PATHOLOGIC CLASSIFICATION

Category	Patients	
	No.	% of 142
Keratinizing squamous cell epithelioma	32	23
Combined Grade 4 undifferentiated carcinoma (lymphoepithelioma, transitional cell carcinoma)	87	61
Miscellany	23	16
Adenocarcinoma	5	
Cylindroma	5	
Lymphosarcoma	5	
Plasma cell myeloma	3	
Rhabdomyosarcoma	3	
Fibrosarcoma	1	
Nonpigmented melanoma	1	
Total	142	100

Table IV

RELATION OF SITE OF PRIMARY LESION TO INVASIVENESS AND CURABILITY

Site in pharynx	Spread				Total Patients	Survived 5 Yr.	
	Superiorly*		Inferiorly†				
	Patients	%	Patients	%		No.	%
Lateral wall	9	24	22	58	38	14	37
Vault	12	23	36	69	52	15	29
Lateral wall and vault	2	25	6	75	8	3	37
Anterior vault and choanae	2	29	2	29	7	1	14
Posterior wall	4	40	3	30	10	3	30
Extensive	5	29	8	47	17	3	18
Indeterminate	6	60	6	60	10	4	40
Total	—		—		142	43	30

* Invasion superiorly with either roentgenographic evidence of bone destruction of floor of middle fossa or involvement of 1 or more cranial nerves.

† Palpable involvement of regional deep jugular cervical lymph nodes.

whether such a subdivision is possible or reproducible and hence have placed all high-grade nonkeratinizing carcinomas in a single group as indicated.

Morphology and Location of Tumor. While some authors have paid particular attention to the morphologic appearance of nasopharyngeal cancers and have given very detailed descriptions of the various types that may develop (ulcerated, lobulated, exophytic nonulcerated, and so forth), we have always thought that the morphologic appearance of these tumors has little relation to the pathologic characteristics encountered at biopsy and little or no relation to the ultimate prognosis. We did not, therefore, attempt any morphologic study of the gross appearance of these lesions. Histologic verification was obtained in each of the 142 cases, the slides having been recently restudied and the diagnoses reconfirmed in all but 15 cases. In these 15 cases the original diagnosis was obtained from slides which had been submitted from elsewhere and examined here but which were now unavailable for review. No cases were included on the basis of "clinical appearance" only.

As in our previous series, we hoped that a study of the location of these cancers would afford some clue to their invasive tendencies. These tendencies were classified according to whether the tumor tended to spread upward or downward. Classification of upward spread was based on roentgenographic demonstration of invasion of the base of the middle fossa, usually in the region of the lacerate foramen, or involvement of either the anterior group of cranial nerves (CN 1 to 6), the so-called petrosphenoid route of Ackerman and del Regato,[1] or the posterior group of cranial nerves (CN 7 to 12), which are involved extracranially along the base of the posterior fossa via the retroparotidean route of Ackerman and del Regato. Involvement of any or all of these 3 groups was classified as invasion superiorly. Classification of downward spread was based on involvement of one or more groups of the cervical deep-jugular chains of lymph nodes.

There seemed to be no particular predilection for tumors at any one site to invade in greater or lesser degree than did those at other sites (Table IV). A later study of the relation of 5 year survival rates to location of the tumor also bears out this nonselectivity as regards the point of origin.

Classification of Nasopharyngeal Car-

TABLE V

CLASSIFICATION OF PATIENTS BY STAGE OF DISEASE

A. Correlation of T-N-M system and stage

	T 1	T 2	T 3	
N 0	Stage I 24 (L 16, D 8)	Stage II 6 (L 4, D 2)	 30 (L 7, D 23)	
N 1	37 (L 11, D 26)	7 (L 1, D 6)	13 (L 0, D 13)	Stage III
N 2	14 (L 2, D 12)	3 (L 0, D 3)	7 (L 2, D 5)	Stage IV

One T 1, N 0, M 1 case (death) not included above.

B. Survival according to stage of disease

Stage	Total Patients	Survived 5 Yr.	
		No.	%
I	24	16	67
II	36	11	31
III	57	12	21
IV	24	4	17
Total	141*	43	30

* One T 1, N 0, M 1 case not included.

cinomas by Stage of Disease. Clinical stage, probably more than any other single factor, has the most bearing on the prognosis of nasopharyngeal cancer, and there is no question that accurate determination of stage is the sine qua non of meaningful reporting of cancer. In our 142 cases, therefore, stage was determined according to the T-N-M system recently formulated by the American Joint Committee for Cancer Staging and End Results Reporting.[3] This staging and its bearing on the ultimate 5 year survival rates are seen in Table v.

However, we believe that this system is inadequate in certain respects. For example, the T-N-M system groups T 2 and T 3 lesions, both without involvement of lymph nodes, in the same stage, thus implying approximately equal survival rates. In our series, 4 of 6 patients with T 2 lesions (lesions confined to the nasopharynx but involving both the lateral and the vault areas) survived 5 years, whereas only 7 of 30 with T 3 lesions (extension outside the nasopharynx proper) survived 5 years; and it would seem most unlikely that lesions that had extended either superiorly to involve the base of the middle fossa or intracranially to involve various cranial nerves would have the same prognostic significance as lesions confined entirely to the nasopharynx.

Nor does this system of staging discriminate between nasopharyngeal lesions that have extended regionally to involve adjacent contiguous structures such as the adjoining hypopharynx, the palate, or the anterior nares, orbits, or paranasal sinuses, and lesions that have extended in a more lethal direction (cranialward) to involve the central nervous system. Further, the T-N-M system of lymph node classification is based primarily on the presence or absence of palpable lymph nodes and their degree of fixation without concern for the number involved and the extent of involvement. The degree of fixation noted is sometimes particularly difficult to ascertain. Certainly staging is dependent upon the training, experience, skill, and impressions of the examiner, and all too often no 2 examiners can agree on the stage.

We have attempted, therefore, to provide an additional system of classification to discriminate between the varying avenues of extension, both regionally and superiorly, as well as to define more precisely the role of multiple lymph node involvement with particular relation to size of the nodal mass and its extension inferiorly into the middle and lower thirds of the neck (Table vi). In both systems, however, the multiplicity of factors concerned is confusing. We have, therefore, attempted yet another schematic representation of the relative effects of the various avenues of extension, with the diagrams geographically oriented to depict better the different

TABLE VI

RELATION OF SPREAD OF DISEASE TO SURVIVAL

Extent of Spread	Patients		
	Total	Lived 5 Yr.	
		No.	%
Nasopharynx only	36	20	56*
Superior spread only	25	7	28
Base of skull, middle fossa	19	5	26
Cranial nerves 1–6	17	3	18
7–12	6	2	33
Inferior spread only (lymph nodes)	68	15	22
Both superior and inferior spread	15	1	7
Total patients with involvement of:			
Base of skull	37	6	19
Cranial nerves 1–6	28	4	14
7–12	12	3	25
Cervical lymph nodes†	81	16	20
Unilateral 1	39	8	
Unilateral 1, 2	3	3	
Unilateral 1, 2, 3	4	0	
Bilateral 1	20	4	
Bilateral 1, 2	11	0	
Bilateral 1, 2, 3	4	1	

* This would be 67%, if 5 patients with regional spread and one with distant metastasis who died within 5 years are not considered.
† Numbers 1, 2, and 3 represent upper, middle, and lower thirds of deep jugular chain, respectively.

routes of dissemination and their effect on survival rates. It is hoped that the shortcomings of such a representation can be overlooked for the sake of conciseness and ease of understanding. Figure 1 shows the relationship of pathologic type of tumor to

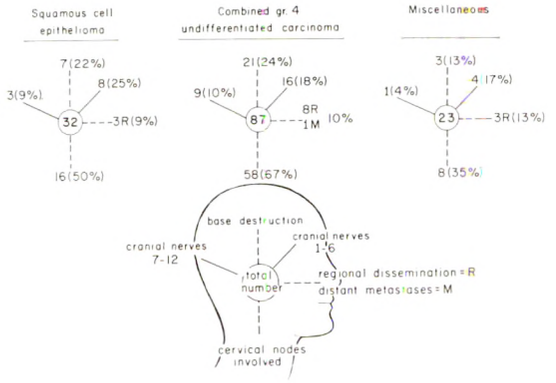


FIG. 1. Schematic representation of relation of pathologic type to dissemination of disease. The lower half of the illustration defines the respective sites of dissemination represented in the 3 parts of the upper half.

dissemination. If we exclude the miscellaneous group, which represents several infrequently encountered pathologic subgroups, we note that both squamous cell epithelioma and the combined Grade 4 undifferentiated carcinoma tend to spread superiorly with about equal facility, whereas the latter group spreads down to involve the regional cervical lymph nodes somewhat more frequently than does the former. However, this difference is not statistically significant. Figure 2 shows the effect of dissemination on survival rates broken down according to the various directions of spread.

TREATMENT RESULTS AND PROGNOSTIC FACTORS

Of the 142 patients, 43 (30 per cent) lived 5 years or more, a result consistent with those reported in most of the recent series of nasopharyngeal cancer (Table VII). Of the 43 five year survivors, 22 have now lived in excess of 10 years. Of the 99 who

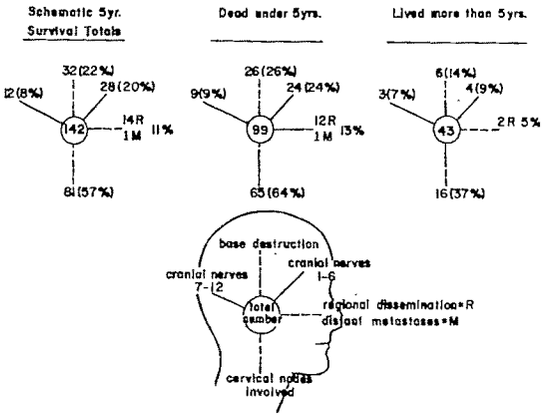


FIG. 2. Schematic representation of 5 year survivals (142 patients). The lower half of the illustration defines the respective sites of dissemination represented in the 3 parts of the upper half.

died of their disease in less than 5 years, 67 per cent died within the first 2 years and 86 per cent died within the first 3 years after start of treatment.

Relation of Sex and Age to Prognosis. Unlike other reported series, our series shows little evidence of a preferential 5 year survival rate for women (29 per cent for males versus 33 per cent for females [Table I]). Except at the extreme ends of the age scale we could find no preferential effect of age on survivorship; 71 per cent of the total 142 patients were in the age group 40 to 69 years and these 3 decades represented 75 per cent of the 5 year survivors. There were, however, no 5 year survivors in the 10 patients less than 20 years of age and only 2 in 10 in the age groups 70 and older.

Relation of Presenting Symptoms to Prognosis. We could attach no particularly ominous significance to any of the chief presenting complaints (Table II). Nor did the duration of presenting symptoms seem to have a bearing on the prognosis (Table VIII).

Relation of Type of Tumor to Survival. Of 32 patients with keratinizing squamous cell epithelioma, 7 (22 per cent) survived 5 years or more (Table IX); 4 of the 7 were alive and well after 10 years or more. This is in contrast to the rate for our series of 1958, in which none of the 17 patients with keratinizing squamous cell epithelioma survived 5 years.

Of 87 patients with Grade 4 undifferentiated carcinoma, 28 (32 per cent) survived 5 years and 15 survived 10 years although 4 of the 15 have subsequently succumbed. Within the group of 87 patients, 66 originally were classified as having lymphoepithelioma, and 23 of the 66 (35 per cent) survived 5 years. Thirteen patients were originally classified as having transitional cell epithelioma, and 5 of these (38 per cent) survived 5 years. An additional 8 patients were unclassifiable as to either of these 2

TABLE VII

RESULTS OF TREATMENT OF NASOPHARYNGEAL CANCER IN VARIOUS SERIES

	Patients	
	Total	Survived 5 Yr. (%)
New and Stevenson[10] (Mayo Clinic, 1943 series)	234	13
Scanlon *et al.*[16] (Mayo Clinic, 1958 series)	88	17
Scanlon *et al.* (Mayo Clinic, present series)	142	30
Wang *et al.*[20]	115	34
Schmidt[17] (Roswell Park)	103	31
Martin and Blady[9]	87	23
Vaeth[19] (Univ. of California)	82	28
Kramer[7]	54	25
Lenz[8]	44	30
Smedal and Watson[18]	39	33
Fitz-Hugh and Wallenborn[5]	37	27

TABLE VIII

RELATION OF DURATION OF PRESENTING COMPLAINT TO SURVIVAL

Duration (mo.)	Patients	
	Total*	Survived 5 Yr. (%)
<3	36	28
<6	71	31
<12	91	28
≧12	32	34

* Patients in each category for whom complaint was recorded.

TABLE IX

RELATION OF PATHOLOGIC TYPE TO SURVIVAL

Type of Lesion	Total Patients	Patients Surviving						
		<1 yr.	1 yr.	2 yr.	3 yr.	4 yr.	5 Yr.	
							No.	%
Keratinizing squamous cell epithelioma	32	17	3	3	2		7	22
Combined Grade 4 undifferentiated carcinoma	87	15	20	14	8	2	28	32
Miscellany	23	5	6	2		2	8	35
Adenocarcinoma	5		2	1			2	
Cylindroma	5	1	1	1		1	1	
Lymphosarcoma	5	1	1			1	2	
Plasma cell myeloma	3						3	
Rhabdomyosarcoma	3	2	1				0	
Fibrosarcoma	1	1					0	
Melanoma	1		1				0	
Total	142	37 (26%)	29 (20%)	19 (13%)	10 (7%)	4 (3%)	43	30

subgroups, and none of the 8 survived 5 years.

Of the group of 23 patients with miscellaneous tumors comprising several pathologic subvariants, 8 (35 per cent) survived 5 years. Surviving 5 years were 2 of 5 with adenocarcinoma, 1 of 5 with cylindroma, 2 of 5 with lymphosarcoma, 3 of 3 with plasma cell myeloma, 0 of 3 with rhabdomyosarcoma, and neither of 1 with melanoma or 1 with fibrosarcoma.

Relation of Primary Site to Prognosis. Apparently no one particular site in the nasopharynx is associated with a graver prognosis than is any other (Table IV). We cannot attach much significance to the lower 5 year survival rate (1 of 7 patients) for those lesions originating in the anterior vault with secondary involvement of the choanae, because of the small numbers involved. It would seem reasonable, however, that the somewhat lower 5 year survival rate for the extensive lesions of the nasopharynx, whose point of origin could not be determined, reflects the more advanced state of the malignant process at the time of original diagnosis. Other than this, the location of the primary lesion does not seem to be of particular prognostic help.

Curability as Related to Stage and Invasiveness. The data in Tables V and VI confirm, as reported by others, a relatively high degree of curability of nasopharyngeal cancer confined to the nasopharynx. Thus, of 36 patients without either superior invasion to involve the base of the skull or cranial nerves or inferior invasion to involve the cervical lymph nodes, 56 per cent survived more than 5 years. Of these 36, however, 5 had regional extension (adjacent lateral hypopharyngeal wall, soft or hard palate) or anterior extension into the paranasal sinuses or orbit, and 1 had apparently localized nasopharyngeal cancer with known chest metastasis at the time of original treatment. If these 6 patients are deleted, the remaining 31 patients, having lesions truly confined to the nasopharynx, have a 5 year survival rate of 67 per cent.

Of 25 patients in whom invasion had occurred exclusively in a superior direction, 28 per cent survived 5 years; this contrasts somewhat with the reports of others in which this degree of invasion connoted an extremely serious prognosis. Of 19 patients with tumors involving the base of the middle fossa, roentgenographically demonstrated, 5 survived 5 years; of 17 patients with involvement of the anterior group of

TABLE X

RELATION OF CRANIAL NERVE INVOLVEMENT TO SURVIVAL

Cranial Nerve Involved	Patients	
	Total	Survived 5 Yr.
1	—	—
2	2	0
3	5	0
4	1	0
5	13	3
6	18	2
7	4	0
8	—	—
9	9	2
10	6	2
11	1	0
12	8	1
Total	67	10

cranial nerves (CN 1 to 6) via the petrosphenoid route, 3 survived 5 years; and of 6 patients with involvement of the posterior cranial group (CN 7 to 12) via the retroparotidean route, 2 survived 5 years.

Of 67 patients in whom the tumor extended exclusively downward to involve the cervical lymph node chains, 22 per cent survived 5 years.

In an additional 14 patients, in whom extension had occurred both superiorly and inferiorly, only 1 (7 per cent) survived 5 years, confirming the grim prognosis reported in our 1958 series for such patients.

When all patients with superior invasion (both alone and combined with inferior invasion) are considered, we found the following: Of 32 patients with roentgenologic evidence of invasion of the base of the middle fossa, 6 (19 per cent) survived 5 years; of 28 with involvement of the anterior cranial nerve group (CN 1 to 6), 4 (14 per cent) survived 5 years; and of 12 with involvement of the posterior cranial nerve group (CN 7 to 12), 3 (25 per cent) survived 5 years.

Table X shows the distribution of patients according to cranial nerves involved by superior invasion. As reported previously and again in agreement with most reported series, the fifth and sixth cranial nerves were the ones most commonly involved when an extension occurred via the petrosphenoid route, and the ninth, tenth, and twelfth were the ones most commonly involved when an extension occurred posteriorly and extracranially via the retroparotidean route. There were no 5 year survivors when cranial nerves other than the fifth and sixth were involved in the anterior cranial group, which must reflect the more advanced stage of the cancers involving more than cranial nerves 5 and 6.

For purposes of study of the prognostic significance of involvement of cervical lymph nodes, the neck region was divided into 3 parts denoting upper, middle, and lower thirds of the deep jugular chain, and involvement was classed as either ipsilateral or bilateral (Table XI). The degree of laterality of the involved lymph nodes seemed to have more influence on the ultimate prognosis than did the level of the involved lymph nodes (5 year survival rate of 24 per cent for unilateral versus 14 per

TABLE XI

RELATION OF CERVICAL LYMPH NODE INVOLVEMENT (81 PATIENTS) TO SURVIVAL

Lymph Nodes Involved*	Patients		
	Total	Survived 5 Yr.	
		No.	%
Unilateral			
1	39	8	21
1, 2	3	3	
1, 2, 3	4	0	†
Total	46	11	24
Bilateral			
1	20	4	20
1, 2	11	0	
1, 2, 3	4	1	†
Total	35	5	14

* Numbers 1, 2, and 3 represent upper, middle, and lower thirds of deep jugular chain, respectively.

† Of 22 patients with unilateral or bilateral involvement of middle and lower thirds of deep jugular chain, 18% lived 5 years.

cent for bilateral involvement), although the difference is not statistically significant.

Effect of Treatment Methods on Prognosis. The effect of two major changes in our treatment policy, the use of higher orthovoltage doses in the earlier years of the period and the switch to cobalt 60 teletherapy in 1954, is shown in Table XII. For the orthovolt group, the larger doses (5,000 r or more) show a significantly higher survivorship ($0.1 < P < .05$) although a similar dose difference for the supervolt group was not observed in our 45 patients. The Chi square homogeneity test for the equality of the 4 survivorship rates in Table XII gives a result of borderline significance ($P = .06$).

The advent of split-dose therapy, however, appeared to have improved considerably the 5 year survival rates for patients with nasopharyngeal cancer. One of us (P.W.S.) has previously published the philosophy behind the results obtained with split-dose radiotherapy for other head and neck cancers,[12–15] and space does not allow a review here. Suffice it to say that, for present purposes, any interruption of from 5 days up to 3 months in the course of a treatment series was considered as representing an example of split-dose therapy. This author (P.W.S.) is now recommending that, optimally, therapy be interrupted to give two equal treatment sessions, each of approximately 12 to 15 days' duration, with a 3 week rest interval intervening between halves of a divided-dose course.

TABLE XII

RELATION OF TYPE OF TREATMENT TO SURVIVAL
5 YEAR SURVIVORSHIP PERCENTAGES*

Tumor Dose	Type of Treatment	
	Orthovolt	Supervolt (cobalt 60)
<5,000 r	17 (41)†	35 (20)
≧5,000 r	44 (36)	25 (36)

* Excluded in the calculations are 9 patients treated by other methods (seeds, topical radium, and so forth).

† Total number of patients on which percentage is based is given in parentheses.

TABLE XIII

RELATION OF CONTINUITY OF RADIOTHERAPY TO SURVIVAL

Method	Total Patients	Survived 5 Yr. (%)
Continuous (conventional fractionated techniques)	114	25 ± .04
Split dose		
1950 through 1960	19	58 ± .11
1950 through 1965	56	49 ± .08
Other (topical radium, seeds, etc.)	9	44
Total (through 1960)	142	30

The reduction in radiation morbidity as well as an apparent increase in biologic effectiveness has been the subject for other reviews and will not be dealt with here.

Of 114 patients treated by continuous radiation methods, 28 (25 ± .04 per cent) survived 5 years or more (Table XIII). An attempt was made to evaluate the effectiveness of split-dose methods, in use here since 1958, by means of 2 groups of patients with nasopharyngeal cancer: (1) 19 patients whose treatment was completed prior to the end of 1960, with a conventional 5 year survival rate of 58 ± .11 per cent and (2) 56 patients, including the 19 in Group 1, representing the total of all patients with nasopharyngeal cancer treated by split-dose methods from 1950 through 1965. The survivorship data for the latter group were calculated by means of nonparametric estimation from incomplete observations, as described by Kaplan and Meier.[6] The 5 year survivorship of this latter group was 49 ± .08 per cent (includes 22 patients still alive less than 5 years after initial treatment). The 95 per cent confidence interval for the 5 year survivorship is $.335 \leq P \leq .645$.

Thus there is a significant statistical difference in 5 year survival between patients treated by conventional continuous fractionated techniques and those treated by split-dose methods whether the comparison is made with the 19 patients on whom complete 5 year survival data are available

or with the 56 patients of the all-inclusive group treated through 1965. Of the 19 patients with a 5 year survival rate of 58 per cent, only 4 had lesions that were apparently localized to the immediate nasopharynx and 1 of these showed evidence of regional spread into the contiguous structures but without spread superiorly to involve the base of the brain or the cranial nerves or inferiorly to involve the cervical lymph nodes. Ten of the 19 had superior extension that involved either the base of the middle fossa or cranial nerves, and 10 had inferior extension that involved the adjoining cervical lymph nodes (several had extensions in both directions). Thus it can be stated that the split-dose group was in no way a preferential or select group.

In both our previous 1958 series and our current one, with one exception, extension of nasopharyngeal cancer both in the superior and in the inferior direction was indicative of an unequivocally fatal outcome. The 1 exception, the following case, is given to illustrate the effectiveness of split-dose methods in the treatment of head and neck cancer.

Illustrative Case. A 29 year old man presented in January, 1959, with a history of severe headaches, diplopia, dizziness, general weakness, nasoregurgitation, difficulty in speech, and prominent bilateral cervical lymphadenopathy of several months' duration. Physical examination revealed a nonulcerating swelling in the left vault which on biopsy proved to be Grade 4 undifferentiated carcinoma, lymphoepithelioma type. Stereoscopic roentgenograms of the base of the skull revealed definite evidence of destruction of the floor of the right middle fossa in the region of the lacerum foramen and neurologic examination revealed paresis of cranial nerves 6 and 9 on both sides and of cranial nerve 5 on the left. The cervical lymph nodes were involved bilaterally down to the level of the clavicle in descending order of size.

Split-dose cobalt 60 teletherapy was given as follows: 14 days of treatment, a rest interval of 20 days, and then 12 days of treatment, for a total tumor dose of 5,000 r with 3,520 r being administered to a left lateral field, 12 by 20 cm. in size, and 3,620 r to a correspondingly opposed right lateral field. The cobalt 60 teletherapy was given at a skin-source distance of 80 cm., treatment being administered at the rate of first 200, then 250, and finally 300 r to one field a day. All visible and palpable evidences of the disease had completely regressed at the time of the re-examination after 3 months. Most unusual, in the next 3 months all evidence of cranial nerve paresis completely disappeared. Unfortunately, metastasis ultimately developed, first in a rib and later in the thoracolumbar spine; these lesions were controlled fairly well with additional radiation therapy. In March, 1964, the patient was living with the primary cancer still under control but with evidence of skeletal and orbital metastasis.

Effect of Extent of Radiation Coverage on Prognosis. Recently, a European visitor expressed surprise and displeasure with what he called the "atavistic tendency on the part of American radiotherapists to employ overly large treatment fields in cases of head and neck malignancy." This is exactly counter to the feeling of most of us that with lesions of the naso-orohypopharynx posterior to the anterior tonsillar pillar, with its extremely high incidence of lymph node involvement, the incidence of geographic miss from inadequate treatment fields is often alarmingly high. In our present series, 57 per cent of patients had palpable cervical lymphadenopathy on initial examination. Subsequent development of lymphadenopathy in additional patients brought this to 65 per cent. Probably, however, this later additional involvement of cervical lymph nodes is underestimated since we do not have a complete follow-up in terms of later disease in this predominantly transient population. It is conceivable, therefore, that the total number of patients developing cervical lymphadenopathy at some point in their disease is considerably higher than the 65 per cent we noted. Hence, we attempted to ascertain whether the extent of roentgen coverage of the involved cervical lymph nodes made a difference in the ultimate salvageability of these patients. We found a 5 year survival rate of 23 per cent when roentgen coverage was limited to the nasopharynx and the

immediate draining cervical lymph nodes in the submastoid region and at the angle of the jaw, 35 per cent when coverage extended over the upper two-thirds of the neck or down to the junction of the middle and lower thirds, and 29 per cent when coverage extended down to the level of the supraclavicular region (Table XIV).

In terms of unilateral *vs.* bilateral coverage of the cervical lymph nodes, the 5 year survival rate was 20 per cent for patients receiving only unilateral coverage and 31 per cent for those receiving bilateral coverage. Although not conclusive proof, these figures support the belief that in the radiotherapy of highly anaplastic lesions of the nasopharynx with a marked tendency to cervical lymph node involvement, it is better to err on the side of fields that are too large than on the side of fields that are inadequate.

One of us (P.W.S.) has believed that split-dose radiotherapy offers a definite improvement in radiobiologic effectiveness over the more conventional, continuous methods of radiation therapy. In nasopharyngeal cancer as well as in other highly anaplastic lesions of the fauces and base of the tongue treated by split-dose methods, it is also possible that the ability to employ larger treatment fields routinely because of the reduction in radiation morbidity is instrumental in reducing the incidence of "geographic miss," thus increasing the apparent effectiveness of split-dose methods.

Effect of Topical or Intracavitary Radium on Prognosis. In our 1958 series, we could detect no evidence whatever that the addition of topical radium to the nasopharyngeal primary lesion added anything to the ultimate salvageability in this group of cancers. Vaeth[19] has stated that "certainly with supervoltage techniques intracavitary irradiation is not indicated and only increases the danger of radionecrosis." In our series of 142 patients, topical radium plaques were employed in 51. The dose was, of course, extremely variable, but averaged between 9,000 and 12,000 r at the surface and approximately 1,500 to 2,000 r at a depth of 1 cm. Thirty-seven per cent of the 51 patients survived 5 years. Of 91 patients not treated with topical radium, 26 per cent survived 5 years. It is doubtful that the differences here are meaningful or express an advantage attributable to topical radium therapy. Eighty-five per cent of the patients given topical radium were from the 6 year period 1950 through 1955. Since then, the use of topical radium has fallen off quite rapidly and is today no longer considered part of the preliminary definitive therapy of nasopharyngeal cancer. It is still used, however, for temporary palliation when a patient returns with local nasopharyngeal recurrence sufficiently limited to permit topical coverage.

TABLE XIV

EXTENT OF RADIATION COVERAGE

Lymph Nodes Irradiated*	Total Patients	Survived 5 Yr.	
		No.	%
Unilateral			
1	2	0	—
1, 2	3	0	—
1, 2, 3	15	4	
Total	20	4	20
Bilateral			
1	37	9	—
1, 2	40	15	—
1, 2, 3	36	11	
Total	113	35	31
Combined			
1	39	9	23
1, 2	43	15	35
1, 2, 3	51	15	29
Total	133	39	29

* Numerals 1, 2, and 3 represent deep jugular chain as follows: 1 = upper third, 2 = middle third, and 3 = lower third.

EFFICACY OF RETREATMENT OF RECURRENT NASOPHARYNGEAL CANCER

Attempts have been made in other series to assess the value of limited retreatment for nasopharyngeal recurrences according to several different parameters, the most common being arrest of further growth for a time (for instance, 12, 18, or 24 months).

Any such palliative effect from limited therapy, however, is extremely difficult to assess, as many of these tumors, by virtue of preliminary heavy definitive therapy, have a more indolent rate of growth than did the primary tumor. We attempted to assess the value of repeated therapy in terms of the more definitive 5 year survival rates (calculated from time of original treatment). Palliative doses of less than 2,500 r, given either as less than vigorous external therapy or as topical radium therapy, were tried in 29 patients with recurrent cancer noted at varying times after definitive primary treatment; none of these patients survived 5 years. More vigorous palliative treatment (more than 2,500 r), however, was tried in 9 additional patients; 6 of these lived 5 years after primary therapy. These 9 patients might have been considered as having split-dose therapy; however, since the time elapsing between treatments was more than 3 months, they did not fit our criteria for split-dose therapy and were not so enumerated.

RADIATION SEQUELA

Only 1 of our 142 patients had a severe radiation sequela: fatal radiation myelitis occurring 6 months after a brainstem-cord dose of 8,100 r delivered in a 40 day period by orthovoltage therapy.

SUMMARY

In 142 patients with primary nasopharyngeal cancer encountered at the Mayo Clinic in the years 1950 through 1960, sex, age, site of primary tumor, presenting symptoms, or duration of symptoms did not seem to bear any relationship to the ultimate salvageability of these patients. The ratio of males to females was 2.4:1. The 5 year survival rate was 29 per cent for males and 33 per cent for females. Seventy-one per cent of the patients and 75 per cent of the 5 year survivors were in the age period 40 through 69 years None of 10 patients less than 20 years of age and only 2 of 10 aged 70 years or more survived 5 years. Site of the primary tumor in the nasopharynx did not seem to carry a prognostic implication: the 5 year survival rate was 37 per cent for lateral wall lesions, 29 per cent for vault lesions, 37 per cent for combined lateral-wall and vault lesions, 14 per cent for lesions of the anterior vault and posterior nares, 30 per cent for posterior wall lesions, and 18 per cent for extensive lesions filling all or most of the nasopharynx.

The pathologic characteristics, as expected, had a definite bearing on the outcome of the disease: the 5 year survival rate was 22 per cent for patients with keratinizing squamous cell epithelioma, 32 per cent for patients with Grade 4 undifferentiated carcinoma (combined lymphoepithelioma and transitional cell group) and 35 per cent for patients with miscellaneous cancers.

Localization of the tumor in the nasopharynx *per se* was associated with a remarkably high 5 year survival rate (67 per cent). Extension upward to involve either the base of the skull or one or more of the cranial nerve groups, as well as extension downward to involve the draining deep jugular lymph nodes, markedly reduced the 5 year survival rate. Thus, the rate was 19 per cent for patients with involvement of the base of the skull as determined *roentgenographically*, 14 per cent for those with involvement of the anterior cranial nerves via the petrosphenoid route, 25 per cent for those with involvement of the posterior cranial nerve group via the retroparotidean route, and 20 per cent for those with involvement of cervical lymph nodes. A 5 year survival rate of 30 per cent for the series is in accord with most of the rates given in the recently reported series.

Dose range, as expected, had a bearing on 5 year survival rates. Thus, patients receiving less than 5,000 r had a rate of 23 per cent, as contrasted to 35 per cent for patients receiving 5,000 r or more. The over-all salvage rates obtained with cobalt 60 teletherapy were approximately the same as those obtained with orthovolt roentgen therapy. The addition of split-

dose methods, however, apparently more than doubled the 5 year survival rates: 25 per cent for continuously treated patients *vs.* 58 per cent for patients treated by split-dose methods. The extent of the coverage of the draining regional lymph nodes appeared to have a minor but definite effect on salvageability of the patients. Coverage of the nasopharynx and immediately adjacent lymph nodes in the upper third of the cervical chain gave a 5 year survival rate of 23 per cent as contrasted with 35 per cent when the nasopharynx plus the upper two-thirds of the neck were covered and 29 per cent when the nasopharynx and entire bilateral cervical chains were covered. Of the patients receiving unilateral coverage of the neck over the site of involved lymph nodes, 20 per cent survived 5 years, in contrast to 30 per cent for the patients receiving bilateral coverage.

Our results in the treatment of nasopharyngeal cancer have improved appreciably in the last decade, the 5 year survival rate having increased from 17 per cent to 30 per cent. It is thought that the addition of split-dose methods will enhance our salvage rates still further.

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THE TREATMENT OF OSTEOGENIC SARCOMA OF THE MANDIBLE*

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THE mandible is a distinctly uncommon location for osteogenic sarcoma. An incidence of 1 to 6 per cent is found in reported series.[10,11,13] Five cases were treated at Walter Reed General Hospital during the period August 12, 1957 through February 12, 1960. Three are alive 5 to 8 years after treatment with no evidence of residual or recurrent disease. This rather impressive survival in a disease usually considered virtually hopeless prompted a review of the pertinent literature. The prognosis is reported to be much better in lesions of the mandible than of the long bones. One or more surgical procedures have usually been carried out sometime during the course of the disease, with or without adjunctive radiation therapy. In a previous report[8] from this institution preoperative radium implantation followed by hemimandibulectomy was advised. The 2 patients reported at that time are long-term survivors and our experience since then substantiates the advisability of this treatment plan. In addition to reporting our additional cases, it is the purpose of the authors to further emphasize the treatment policy which should increase an already acceptable survival.

REPORT OF CASES

Cases 1 and 2. The first 2 cases were reported by Gomez *et al.*[8] in 1960. One of these was again reported by Shira and Bhaskar[16] in 1963 as a 6 year follow-up. Both of these patients are alive and without disease 7½ and 8 years after treatment (Table 1).

Case 3. M.M.M. is a 20 year old female who first noted swelling of her gum in the left lower molar area in October, 1959. Roentgenographic examination revealed a destructive lesion in the mandible. The first molar was removed and biopsy of the surrounding tissue was performed. The biopsy was interpreted as osteochondroma. There was good healing of the biopsy site but on January 1, 1960, swelling developed again in the area along with pain which had been increasing since the biopsy. The patient was sent to Walter Reed General Hospital at that time. On February 12, 1960 there was noted slight swelling of the left mandibular area and a 2.5× 2×0.5 cm. mass opposite the first and second molars on the left was easily seen (Fig. 1). There was no lymphadenopathy and no other abnormalities were detected. On February 13, 1960, a biopsy was interpreted as osteogenic sarcoma. On February 24, 1960 nine teeth were removed in the area and a radium implantation was performed in the mandible (Fig. 2). The implant remained 117 hours for a dose of 11,244 r maximum. After removal of the implant, the patient was sent home and returned on March 21, 1960. Five days later a left hemimandibulectomy and en bloc dissection of the left digastric triangle were performed.

The tissue removed at surgery revealed osteogenic sarcoma with radiation osteitis and osteomyelitis of the anterior end of the mandible. On February 4, 1962 there was no evidence of residual disease. In the ensuing years, a number of plastic procedures have been performed for reconstruction of the mandibular area and surrounding soft tissues. The patient is in good health at the time of this report.

Case 4. G.L.K. was a 26 year old male who first noted soreness and bleeding of the gums in October, 1960. Pain in the lower jaw increased and at the end of November, 1960 he went to a dentist and was treated for infection of the gum with improvement in his symptoms. Shortly thereafter, the pain again began to increase and he noted a red mass in his right lower gum area.

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TABLE I

SUMMARY OF TREATMENT AND RESULTS

Case	Age	Irradiation	Surgery	Results
1. N.M.S. female[8,16]	18	Radium implant 7,910–10,900 r in 4.85 days	1. Tooth extraction, local excision prior to irradiation 2. Right hemimandibulectomy 16 days after radium implantation	Living without disease $7\frac{1}{2}$ years after surgery
2. L.K. female[8]	32	Radium implant 7,320–11,040 r in 5 days	1. Two biopsies with curettage prior to irradiation 2. Left hemimandibulectomy 1 day after radium implantation	Living without disease 8 years after surgery
3. M.M.M. female	20	Radium implant 11,244 r in 4.86 days (Fig. 1 and 2)	1. Two biopsies prior to irradiation 2. Left hemimandibulectomy 4 weeks after radium implantation	Living without disease 5 years after surgery
4. G.L.K. male	26	Radium implant 8,300–10,000 r in 3.1 days; 9,370 r to smaller plane in 8 days (Fig. 3, *A* and *B*)	1. Tooth extraction, 2 biopsies, sequestrectomy prior to irradiation 2. Total mandibulectomy 3 weeks after radium implantation	Died of widespread metastasis 3 years 8 months after surgery; *no* local *recurrence*
5. P.E. female	21	Postoperative roentgen therapy 4,000 r maximum to recurrent disease	1. Biopsy, subtotal hemimandibulectomy, 2 revisions of mandibulectomy	Died of massive recurrent tumor and metastasis 16 months after surgery

In December, 1960 he noted that the teeth in the lower jaw were becoming loose and several were extracted when he again visited the dentist. Burning sensations in the mandible remained and the gingiva became dark colored with some fluid drainage. On January 10, 1961, the dentist was again consulted and there was suspicion of osteomyelitis. Biopsy was per-

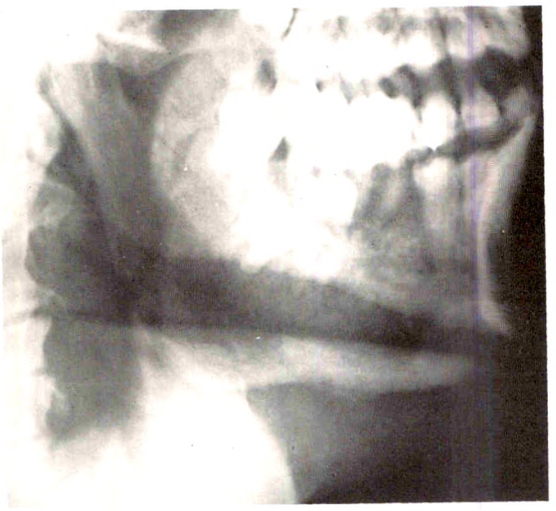


FIG. 1. Case 3. The irregular mottled sclerotic lesion is seen filling the socket of the recently removed first molar. Periosteal new bone formation is visible beneath the inferior margin of the mandible.

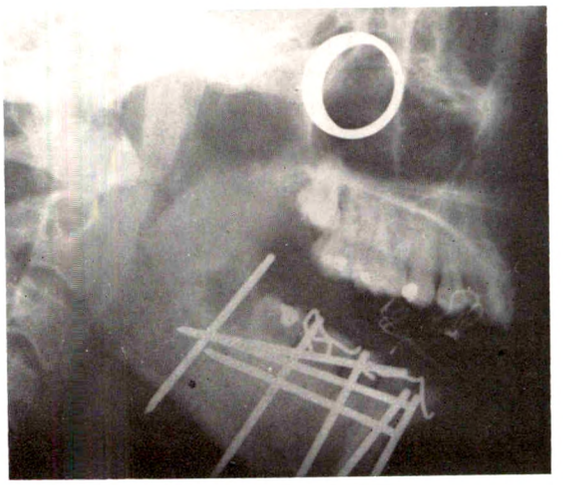


FIG. 2. Case 3. Lateral view of the radium implant. This is the only roentgenogram available for reproduction. The horizontal needles represent an outer plane in a somewhat less than ideal configuration and were removed early.

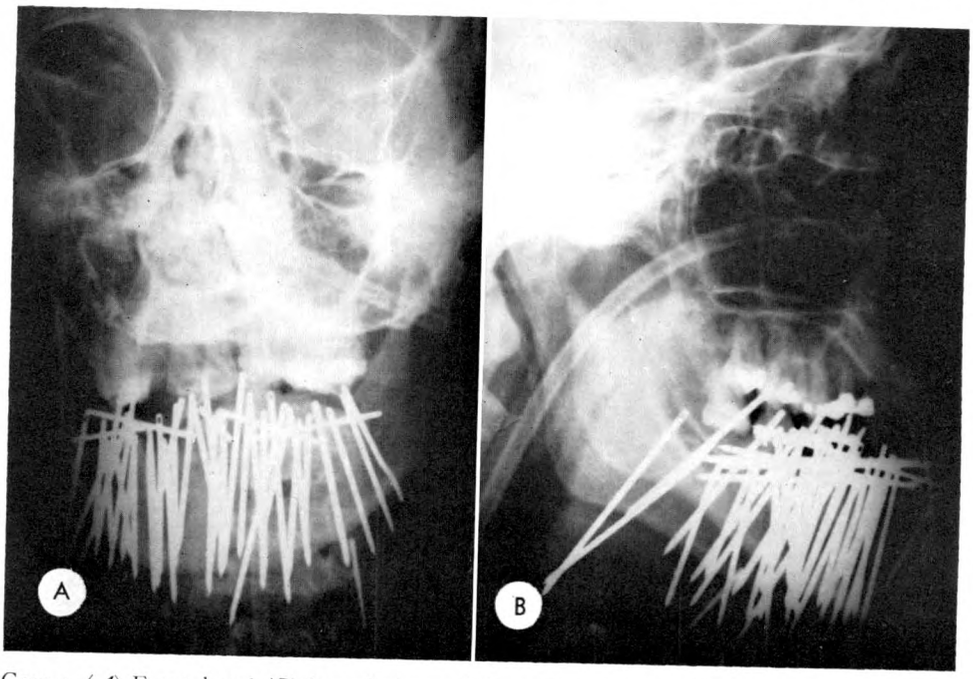


FIG. 3. Case 4. (*A*) Frontal and (*B*) lateral views of the radium implant. The "broken needle" in the soft tissue of the neck on the left is a dental burr lost at the time of the implant. It was removed later with the jaw.

formed the next day and a diagnosis of ossifying fibroma was made. On January 19, 1961 the patient was admitted to a hospital in New York for the treatment of osteomyelitis of the mandible. Four days later a white mass was noted growing on the buccal plate of tooth #23. On January 25, 1961, five teeth were removed in the lower mandibular area and sequestrectomy was done. A specimen of moth-eaten bone was sent for pathologic examination and the diagnosis of osteogenic sarcoma of the mandible was established. On February 20, 1961, the patient was admitted to Walter Reed General Hospital for treatment. At that time he had a hard, tender mass on the right mandible, about 6 cm. long and 5 cm. wide, extending across the floor of the mouth to the midline. A similar mass was noted in the left lower bicuspid area which is probably an extension of the right mass along the mentum.

On March 7, 1961, under general anesthesia the 6 remaining lower teeth were extracted and radium needles were placed in 31 holes drilled into the tumor (Fig. 3, *A* and *B*). Seventy-five mg. of radium was used and remained in place for 3.1 days for a minimum dose of 8,300 r and a maximum dose of 10,000 r. On April 10, 1961, a total mandibulectomy, gastrostomy, and tracheostomy were performed. The tongue was also removed at the time of surgery. The patient made a relatively uneventful recovery and was sent on convalescent leave in July of 1961. By August of 1961 he had lost a total of 70 pounds and had been subsisting on formula feeding by the gastrostomy. The patient did quite well despite marked disfigurement and on July 28, 1964 a note was received from the patient stating that he did not intend having any plastic work done until a 5 year follow-up was complete. He was wearing a paper face mask because of constant drooling.

In October, 1964 he became dyspneic and a chest roentgenogram revealed pulmonary metastases. Dyspnea gradually worsened and he developed increasing edema of the legs, joint pains, and cough. He died on December 9, 1964, three months after the appearance of the metastases. Autopsy revealed metastatic osteogenic sarcoma in the left lung, pleura, liver, pericardium, kidney capsules, and left adrenal gland. There were multiple pulmonary emboli which were the immediate cause of death. There was no evidence of recurrence in the neck or at the primary site.

Of interest is the comment on the original biopsy report which stated, "This tumor in this

location is said by some to have a somewhat better prognosis than the same tumor elsewhere and by others to act in about the same manner. In any case, the prognosis is poor and the tumor will probably recur and kill the patient within two to three years."

Case 5. P.E. was a 21 year old female who noted loosening of the teeth in the right molar area in March of 1961 while she was in Germany. She first complained to a dentist about this in June, 1961. Roentgenographic examination at that time revealed an osteolytic area in the mandible which was biopsied, the diagnosis being chondrosarcoma. On June 29, 1961 a subtotal right hemimandibulectomy and right supra-omohyoid dissection were performed. The diagnosis rendered on the operative specimen was osteogenic sarcoma. Report of this biopsy was not available until October 28, 1961 and on this report there was a statement that the proximal section had residual tumor and further resection was indicated. On November 2, 1961 an additional portion of the right mandible was removed including the coronoid and condyloid processes and the remaining body with surrounding soft tissue. There was residual osteogenic sarcoma in this specimen as well. On November 28, 1961 the patient was transferred to another hospital with the recommendation of further resection of the mandible and soft tissues in the area. Roentgenograms showed invasion of the distal portion of the resected area. On December 12, 1961, the right mandible was resected to the left cuspid area including the entire symphysis and much of the surrounding muscle and soft tissue. Pathology reports revealed residual tumor extending to the resected margins.

The tumor rapidly recurred and continued to grow despite courses of external roentgen therapy and intra-arterial metasarcolysin infusion. In October the tumor had grown so that it protruded from the right ear canal and infiltrated the skin of the right neck. Edema of the face and neck developed and she began to experience respiratory difficulty. She died suddenly after an episode of acute respiratory distress on October 26, 1962.

Autopsy revealed tumor in the neck, carotid sheath, around the trachea and esophagus, and extending toward the right hilus. There were metastatic deposits in the right lung and hilus. Tumor had spread up to the pterygoid fossa and posterior cranial fossa. The temporal lobe was adherent to tumor growing through the temporal bone. There were metastases in the temporal lobe and meninges of the posterior fossa. The final comment on the autopsy protocol read as follows: "This case illustrates the usual inextricable, fatal course of osteogenic sarcoma."

COMMENT

These cases follow the experience of others in showing definite differences in the clinical presentation and subsequent course when comparison is made with patients having the long bone lesion. Some of these differences merit special discussion.

AGE

Patients with the mandibular lesions are older. Most of the cases occur after 25 years of age; in Kragh and co-workers' series[10] of 19 patients the average age was 33.2 years. Lesions in the extremities occur mostly between 10 and 25 years of age. Brody and Fry[2] investigated the effect of age on survival in their series of 63 cases which excluded the facial bones. The 5 year survival of patients less than 20 years of age was 6 per cent, but was 20 per cent for the patients older than 20 years. Coventry and Dahlin,[5] in their much larger series, however, compared the groups of patients below and above 30 years of age and stated that the younger group appear to live longer. The same trend is notable in Kragh and co-workers' series of mandibular lesions since 2 of 5 patients under 20 survived, but only 4 of 14 over 20 were alive after 5 years. Two of our cases were in the younger group and both are survivors. The 2 that died were over 20 years of age.

The evidence is certainly far from conclusive, but there is reasonable doubt that the increased average age of the mandibular patients is related to their increased survival.

DIAGNOSIS

Roentgen signs are either absent or nonspecific in the mandibular lesions.[14] In the long bones the roentgen signs seldom fail to raise the suspicion of a malignant process.

The histologic diagnosis of osteogenic sarcoma should not be a problem for the pathologist in most instances. The lack of uniformity in defining the histologic criteria of the lesion which characterized the study of this tumor in earlier years has largely disappeared. The diagnosis is based upon the appearance of neoplastic bone and osteoid within a malignant neoplasm of connective tissue.[5,7,12] Anything less is not osteogenic sarcoma. Other malignant tissue may be present in various proportions. At this hospital, the diagnosis is made only if the majority of the tumor cells are producing bone and osteoid.

One reason for the better prognosis in the mandibular lesions may be a better differentiated tumor in this location. Certainly, there is seldom a question of whether or not the long bone lesions are malignant, but a common factor in the history of nearly all the mandibular group is the diagnosis of some benign condition such as fibrous dysplasia, giant cell reparative granuloma, chondroma, osteoblastoma, or osteoma on the first biopsy.[10,13] Kragh *et al.*[10] state that in their patients the better differentiation was indeed apparent.

CAUSE OF DEATH

The clinical course of mandibular cases treated unsuccessfully is usually less than 3 years.[5,9,10,13] Death is due to local recurrence, inanition, and possibly intracranial extension. Pulmonary or otherwise widespread metastasis is seldom seen without local recurrence. Many patients undergo several local operative procedures for removal of persistent and recurrent tumor. Although this long period of apparent containment should make surgery more feasible, the extent of the original lesion is either underestimated or the tumor is spread by the operation. It is possible, however, to obtain long survival in spite of multiple operative procedures.

In the long bones, local recurrence is seldom seen after a definitive surgical ablation has been performed. Widespread metastases are the cause of death in nearly every patient, and the appearance of the metastases, if not present when the patient is first seen, can be expected within months after definitive therapy and usually kills the patient within 2 years.[12] Late metastases do occur, however, even with the most anaplastic primary lesions, and survival after local resection of solitary metastasis to the lung has been reported.[6]

All of our survivors had preoperative radium implantation of the primary lesion in the mandible. The doses delivered were far in excess of the usual doses thought to be tumoricidal. One of the patients who died (Case 5) did not have the preoperative radium implantation because the diagnosis of osteosarcoma was not made until after definitive surgery had been performed on what was thought to be chondrosarcoma. This patient had extensive local recurrence which could not be controlled and she died of the recurrence within 16 months of the first operative attempt. The other death (Case 4) occurred from distant metastasis nearly 4 years after the first therapeutic attempt, using the preferred preoperative radium implantation. There was no evidence of recurrence at the primary site or in the neck.

TREATMENT

The successful management of patients with osteogenic sarcoma of the mandible is a combined cooperative effort of the departments of head and neck surgery, dental surgery, and radiation therapy. As soon as the diagnosis is confirmed by biopsy, the radium implantation is undertaken. Teeth on the side of the jaw affected must be removed. This is done under general anesthesia and as soon as bleeding is controlled, holes are drilled into the mandible for placement of the radium needles. An orthopedic drill or dental burr is used for this purpose. The needles are sewn in place and their position is confirmed by stereoscopic roentgenograms of the jaw. Patients tolerate the procedure quite well and require little, if any, analgesia after the first day. A soft diet or liquid diet will sustain

the patient for the 4 to 5 day period during which the needles are in place. Removal of the implant is usually accomplished without difficulty under mild sedation at the calculated time. The definitive surgical procedure should follow the removal of the implant as soon as practicable, ideally the following day.

An intense radiation mucositis develops 10 to 14 days after removal of the implant, but this should not hamper a delayed surgical effort since most of the heavily irradiated tissue is to be removed along with the tumor. The amount of tissue removed with the hemimandibule is variable and depends on the size of the primary tumor. Recovery from surgery has been uneventful. After the operative site has healed, plastic reconstructive procedures are planned which leave the patient with minimal cosmetic deformity.

DISCUSSION

Osteogenic sarcoma of the mandible is unique in its clinical course. Contrary to some reports indicating a high mortality,[1,13,17] the survival is significantly greater than might be expected in patients with long bone lesions. The greatest reported survival for osteogenic sarcoma in large series[5,11] is in the vicinity of 20 per cent. In smaller series, 5 year survival is generally reported as being between 5 and 10 per cent. The disease is usually fatal within 2 years. In Kragh and co-workers' series of mandibular lesions, 6 of 19 patients were alive 6–28 years after treatment (31.6 per cent). None of the survivors had definitive preoperative irradiation to the mandible. All of the patients who proved treatment failures were dead within 3 years.

Failure in the management of mandibular cases is manifested by local recurrence of the disease. Even then salvage is possible because of the fortunate lack of early metastasis. Wide surgical excision of the lesion is effective and practicable in nearly all patients and should consist of no less than a hemimandibulectomy with en bloc removal of contiguous structures. Preoperative irradiation by means of a high dose radium implantation of the primary lesion appears to be effective in preventing local recurrence. None of our cases in which such an implant was employed had local recurrence. The patient who died of late metastasis had an immense tumor, but no residual in the head and neck could be found at autopsy. The radiation has its effect presumably in devitalizing the tumor cells so that they are less likely to result in a recurrent growth if spilled at surgery. A possible effect on the prospective tumor bed reducing the likelihood of growth support for the tumor cells can also be postulated. The definitive surgical attack should follow the radium implantation after a rest period of no longer than 1 month. It is generally agreed that irradiation alone cannot be expected to result in long term survivals. The operative specimens in our cases all showed viable tumor despite the high doses given. External irradiation has no place in the curative effort but can afford significant palliation when the need arises.[3]

CONCLUSION

Osteogenic sarcoma of the mandible is a rare lesion with a prognosis much better than is generally realized. Cure is definitely within the realm of probability, and the treatment program should be undertaken with enthusiasm. The minimum therapeutic effort should consist of a large dose radium implantation of the lesion followed as soon as practicable by a wide hemimandibulectomy. With this regimen, it is anticipated that major cause for failure, *i.e.*, local recurrence, can be virtually eliminated and that survival will be further improved.

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COBALT 60 TELETHERAPY OF EARLY CARCINOMA OF THE VOCAL CORDS*

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THE conservative curability of carcinoma of the larynx by radiotherapy has been established for over 40 years;[4] the relatively better results obtained in the earlier lesions, limited to the vocal cords, have been variously recognized and reported.[1,2,3] The utilization of supervoltage roentgen therapy and cobalt 60 teletherapy has brought about the possibility of further improvement of results, particularly in these early carcinomas, to a point of near perfection.

The principal assets of cobalt 60 teletherapy consist in the possibility of irradiating the limited area of the neoplastic involvement to a relatively high dose of radiation with no, or negligible amount of, radioepithelitis of the mucous membrane and no radioepidermitis of the skin. These advantages favor further the possibility of greater intensity in daily irradiation and shorter over-all duration. The higher dosage, more homogeneously distributed, and the greater intensity of daily irradiation may be responsible for the better results. Because of the rather sharp delimitation of the field of irradiation, the patients do not suffer from any degree of dysphagia during or after the course of treatments.

CLINICAL MATERIAL

This report is based on 16 consecutive cases of histologically proven squamous cell carcinomas of the vocal cord treated at the Penrose Cancer Hospital from 1955 to March, 1961. Nine of these patients presented lesions limited to one vocal cord and 1 had extension to the commissure and opposite cord but none had any impairment of movements (T_1, N_0, M_0, of the Committee on Radiation Therapy Studies); 5 others had unilateral lesions and 1 involved the anterior commissure and opposite cord, with partial limitation of cord movements (T_2, N_0, M_0, of the Committee on Radiation Therapy Studies).

Thirteen of the patients were of the male and 3 of the female sex; the youngest patient was 37 years old and the oldest 81, with an average age of 57.8 years. Hoarseness was the only symptom in all cases and had been present for 1 month to 2 years before the diagnosis was established. Twelve of these carcinomas were well differentiated and 4 were found to be poorly differentiated.

TECHNIQUE OF TREATMENT

All of the patients were treated with cobalt 60 teletherapy at 80 cm. source skin distance. The patients were placed in dorsal decubitus with the shoulder on the treated side raised and supported with sand bags, the face turned, extended and adequately fixed in the opposite direction. Two lateral fields of entry, measuring 4.5×4.5 cm. were utilized (Fig. 1). This size field covers generously the area of potential involvement; it is important, however, that it be adequately centered and that the patient be well immobilized for the duration of treatments. The incident beam of radiations was directed laterally with a slight anteroposterior inclination of about 15 degrees.

The daily dose administered was of 300 to 350 r on the surface of the skin, alternately to each of the two fields to a total of 3,500 to 4,000 r to each lateral surface in a total of 25 to 32 days. The calculated dose at the mid-point of the larynx, in the sagittal plane, was approximately 6,500 to 7,000 r. A dosimetric study revealed a rather homogeneous distribution of radiations throughout the larynx (Fig. 2).

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FIG. 1. Lateral roentgenogram of the larynx with superimposed limits of field of irradiation.

RESULTS

In spite of the fact that our irradiation is more intensive in daily dosage and that the total amount of radiations administered is greater than previously given with conventional roentgen therapy, the mucous membrane and skin reactions are minimal and of little consequence. With the use of very high daily dosage, edema of the arytenoids may occur during the course of, or following, treatments, on the affected and/or on the opposite side. In some instances we have had recourse to administration of antibiotics, during the period of edema, to avoid possibility of necrosis.

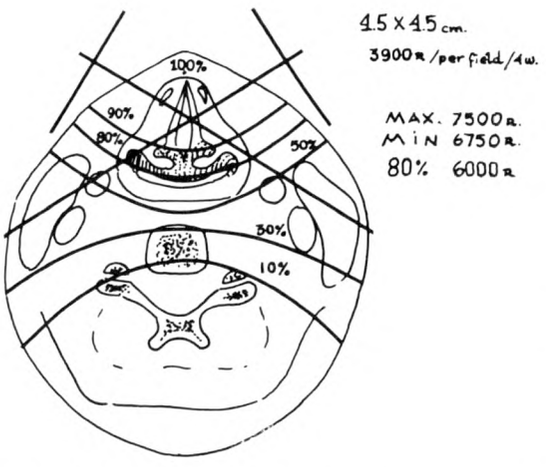


FIG. 2. Distribution of dose administered through two anterolateral fields.

One of the 16 patients treated died of intercurrent disease $4\frac{1}{2}$ years after treatment; at autopsy, no evidence of residual or recurrent disease was found in the larynx. Only 1 patient developed a local recurrence; he had a poorly differentiated carcinoma. A total laryngectomy was performed without any technical difficulty, but the patient died with pulmonary metastases, $3\frac{1}{2}$ years after the initial treatment. Another patient developed a cervical metastasis for which a radical neck dissection was carried out; the patient remains well over 5 years and there has been no local recurrence.

In only one instance in this series did we have relatively important untoward effects; it was the case of a female patient who was treated rather intensively; she developed necrosis of the endolarynx necessitating a tracheostomy. The necrosis eventually healed and the patient remains well over 8 years after treatment.

With the exception of the one patient who presented a local recurrence and the one who died of intercurrent disease, all other patients are living and free of disease, from 5 to 10 years after treatments. Five patients recovered a normal voice promptly after completion of treatments; 8 others kept a slightly hoarse voice which has improved with time; 1 has kept a persistent moderate hoarseness and 1 (the female patient who suffered radionecrosis) has remained markedly hoarse.

SUMMARY

1. A small series of 16 consecutive cases of squamous cell carcinoma of the vocal

cords and anterior commissure is presented.

2. The patients were treated with cobalt 60 teletherapy with an average dose of 6,500 to 7,000 r at the mid-sagittal point of the larynx in 25 to 32 days.

3. Only 1 patient in this series showed a local recurrence after treatment.

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PRESERVATION OF THE LARYNX IN THE SURGICAL TREATMENT OF CANCER, RECURRENT AFTER RADIATION THERAPY*

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IT IS without question desirable to preserve the larynx whenever this can feasibly be done in the course of treatment of cancer in, or adjacent to this organ. However, the advisability of saving the larynx when one is dealing with a recurrent lesion is subject to question. Admittedly, the wider the resection of a cancer, the less the likelihood of local recurrence. However, all cancers do not have the same proclivity for invasiveness and lymphatic spread, and if it is possible to identify those cancers which have limited tendency for extension, it should be possible to do more conservative operations on these cancers.

Cordectomy or partial laryngectomy is a recognized and effective means of treatment for the localized previously untreated cancer of the larynx. The usual treatment for a cancer of the true cord, recurrent or residual following irradiation, has been total laryngectomy.

At the M. D. Anderson Hospital, small cancers of the true vocal cords are almost routinely treated by external irradiation. This has resulted in a very satisfactory rate of local control with preservation of normal function. From 1948 through August, 1964, 300 patients have been treated with a local recurrence rate of 12 per cent. Most of the recurrences were treated by total laryngectomy, but on examining a number of the specimens it appeared as though the lesion were still localized, and that a surgical procedure of lesser magnitude might have been equally effective.

It appeared that if a limited surgical procedure for recurrences following irradiation were to succeed, the following criteria should be met: (1) The cancer must have been localized originally; (2) regional lymph node metastasis should not be a dominant feature of the disease; and (3) the original extent of the cancer should be circumscribed by the surgical procedure.

Since these criteria were fairly restrictive, the number of patients who seemed to qualify has been small. Nevertheless, since the object of cancer therapy is to cure as many patients as possible with the least amount of disability, our experiences in exploring the possibility of preserving the larynx may merit examination.

Our initial cordectomy for residual squamous cell carcinoma of the larynx was done in 1960, and 6 additional cordectomies have been performed, 1 on a patient whose irradiation treatment was given at another hospital. In 5 of the 7 patients, the tumor dose was between 5,500 and 6,050 rads, but in the last 2 patients, tumor doses of 6,960 and 7,050 rads were delivered. Since the cordectomies were done following laryngofissure for exposure, we were not certain whether or not satisfactory healing would take place. To date, healing has not been a problem except in 1 patient who received a tumor dose of 6,960 rads, and in whom there is a question of solid union anteriorly. Representative case histories follow.

ILLUSTRATIVE CASES

CASE 1. A 60 year old male was admitted on October 27, 1957 with a history of hoarseness of 1 year's duration. Biopsy of the larynx showed squamous cell carcinoma, Grade 1. Examination of the larynx showed a verrucous lesion involving most of the surface of the left cord with good mobility of the cord. Between October 2 and November 22, 1957, the patient received a tumor dose of 5,650 rads through 5×4 cm. fields, employing the cobalt 60 unit.

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In 1959 a leukoplakic lesion appeared on the left cord. Three biopsies over a 7 month period were reported to show only chronic inflammation and leukoplakia. However, the lesion progressed and it was felt that the cord should be removed. A laryngofissure and left cordectomy were done on August 25, 1960 for a lesion which was reported by the pathologists to be carcinoma *in situ*. When the patient was last seen on February 11, 1966, there was no evidence of disease and the voice was good.

CASE II. Hoarseness of 3 months' duration led this 54 year old, 2 package of cigarettes a day smoker to seek attention on September 3, 1965. Examination of the larynx showed the right vocal cord to be thickened, with slightly impaired mobility. Following biopsy of the larynx which was reported to show squamous cell carcinoma, Grade II, the patient was treated by the cobalt 60 radiation unit through a 4×3 cm. port to a tumor dose of 7,040 rads in 6 weeks. In January, 1966 it appeared as though there were residual cancer in the larynx, and a laryngofissure and right cordectomy were done on January 26, 1966. Pathologic diagnosis was squamous cell carcinoma, Grade II. Wound healing was entirely uneventful. Recent examination showed no evidence of recurrence and the voice was good.

One patient died 2 years following surgical resection of a vocal cord cancer residual after irradiation. Postmortem examination showed death to be due to bronchogenic carcinoma, but there was no microscopic evidence of recurrent cancer of the larynx.

In this small series there has been one recurrence following cordectomy with successful treatment by laryngectomy.

CASE III. A 74 year old male was seen on March 18, 1960 with hoarseness of 8 weeks' duration. He had been a heavy cigarette smoker from age 16 to 68 years. Examination showed leukoplakia of the right vocal cord plus what appeared to be early invasive tumor. Several biopsies showed only atypical squamous epithelium, but it was elected to irradiate because of the typical appearance of the lesion. From March 23, to April 19, 1960 through a 3.5×3.5 cm. field using the cobalt 60 unit, the patient received a tumor dose of 5,500 rads. On March 19, 1962 a biopsy of an elevated mass on the right cord was reported to be leukoplakia. The lesion progressed and on April 25, 1962 a right cordectomy was done. The pathologic report showed early invasive squamous cell carcinoma with free margins. On October 9, 1962, a biopsy of a lesion of the anterior commissure showed squamous cell epithelioma, Grade I. The patient refused surgery until September 11, 1963, by which time the cancer had grown through the anterior commissure to invade the skin of the anterior neck. The pathologic examination showed squamous cell carcinoma, Grade II, with local extension to soft tissues and skin. No evidence of recurrence was noted when the patient was last seen on January 7, 1966 (Fig. 1, *A*, *B* and *C*).

Comment. Conclusions which may tentatively be drawn from this group of cases are: (1) Interpretation of biopsy material and prediction of behavior on the small amounts of tissue available may be difficult. This is particularly so following irradiation; (2) should recurrence develop following cordectomy after irradiation, a laryngectomy could probably be done with relative ease; and (3) wound healing with a midline incision for laryngofissure following irradiation is satisfactory.

More controversial would be the decision to save the larynx in the treatment of recurrent lesions after radiation therapy for cancer other than those on the true cord. These cancers have a more aggressive behavior biologically with an increased incidence of lymph node metastasis. Our experience with the problems is illustrated in the following three cases.

CASE IV. On May 10, 1963, a 49 year old male was seen because of a lump in the left lower neck of 1½ months' duration. Examination showed a small lesion of the left aryepiglottic fold and arytenoid. There was a 2.5 cm. left midjugular lymph node. Biopsy of the larynx showed squamous cell epithelioma, Grade II. Between May 22, 1963 and June 20, 1963, a tumor dose of 6,000 rads was delivered to the primary lesion with 18 mev. electron beam unit through an 8×6 cm. field and the same tumor dose was delivered to the lymph node on the 12 mev. electron beam unit through a 4 cm. circle. The pathologic report on a left neck dissection done

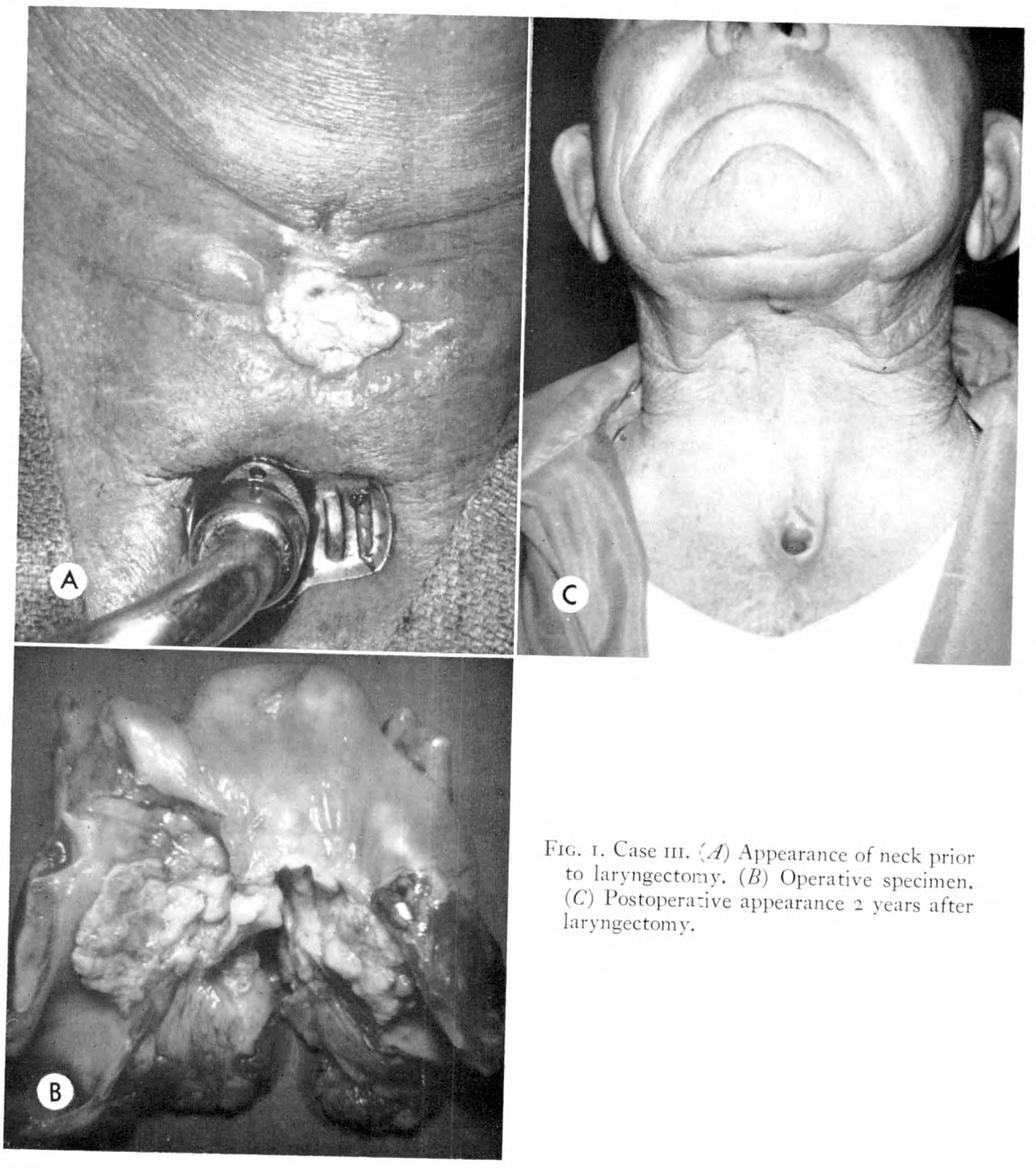


FIG. 1. Case III. (*A*) Appearance of neck prior to laryngectomy. (*B*) Operative specimen. (*C*) Postoperative appearance 2 years after laryngectomy.

on August 26, 1963 showed metastatic squamous cell carcinoma in one lymph node. Biopsy of a suspicious lesion on the left aryepiglottic fold on April 24, 1964 also revealed squamous cell carcinoma. Resection of the left arytenoid region and left aryepiglottic fold on May 11, 1964 demonstrated squamous cell carcinoma. Follow-up study of April 8, 1966 showed that the patient swallowed and spoke normally.

CASE V. A 67 year old male physician was seen on December 3, 1963 with a history of sore throat of 4 months' duration. Biopsy before admission showed squamous cell epithelioma, Grade II. Examination disclosed a superficial area of ulceration, 2 cm. in diameter, in the left base of tongue and vallecula. No clinically enlarged lymph nodes were evident. From December 3, 1963 to January 17, 1964, using

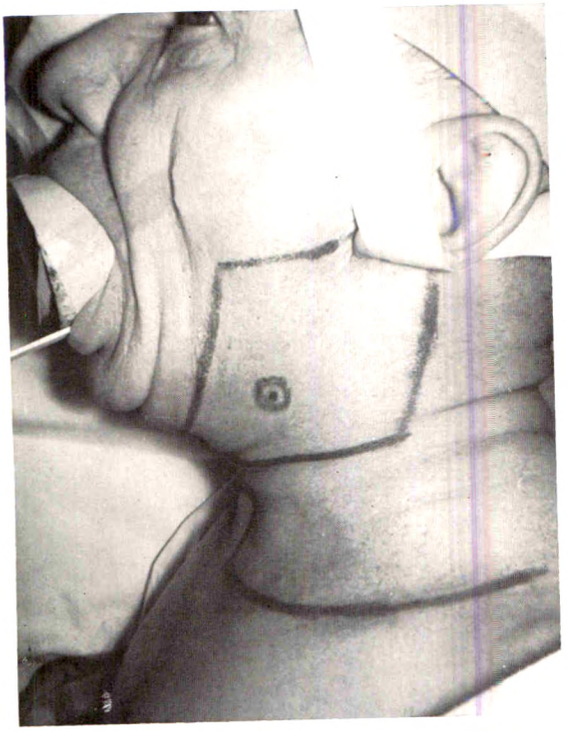


Fig. 2. Case VI. Outline of treatment fields.

the cobalt 60 unit, both sides of the neck from the mandible to the clavicle, including the base of the tongue, were treated to a tumor dose of 6,050 rads. On February 3, 1965, a resection of the left base of the tongue for recurrence was done through an infrahyoid incision. The pathologic examination revealed squamous cell carcinoma with margins free of tumor. Wound healing required 6 weeks, but when the patient was re-examined in January, 1966, the voice was normal and he swallowed without difficulty.

Case VI. A 62 year old male was referred on October 2, 1964 for treatment of a cancer of the left base of the tongue, with left subdigastric lymph node metastasis. Examination showed a 1.5 cm. mass in the left base of the tongue and a 2 cm. left subdigastric lymph node enlargement. Radiation treatment extended from October 7, 1964 to December 1, 1964, with both sides of the neck from the clavicle to the jaw being irradiated on the cobalt 60 unit, to a tumor dose of 6,500 rads (Fig. 2). Recurrence was apparent 4 months after completion of treatment On April 19, 1965, resection of the base of the tongue, epiglottis and hyoid, and right upper neck dissection with creation of pharyngeal stoma were done. The pathologic diagnosis was squamous cell carcinoma in fibroconnective tissue from the right upper neck. A left upper neck dissection was done on May 17, 1965 and an acromiothoracic tube pedicle was created. The pharyngeal stoma was closed with an acromiothoracic tube pedicle on September 8, 1965. On March 8, 1966, there was no evidence of recurrence, the voice was normal, and the patient swallowed with only slight difficulty.

Comment. The advisability of preservation of the larynx in the latter 3 patients remains to be seen, since the follow-up period is too short. However, in Case VI,* it was felt that the usual procedure of bilateral neck dissection, laryngectomy and resection of the base of the tongue could not be done without almost prohibitive morbidity in view of the heavy radiation received. These 3 cases do show that it is possible to do limited procedures about the irradiated larynx with satisfactory wound healing and retention of normal voice and swallowing function.

SUMMARY

Ten cases of cancer in or about the larynx, recurrent after irradiation, in whom limited surgical procedures have been done were observed. In 7 of these patients, the initial cancer was in the true cord region. The results in these patients have been encouraging to date. In 2 of the other patients, the cancer was in the base of the tongue, and in 1, on the arytenoid and aryepiglottic fold. It is too soon to determine whether a limited procedure will be a satisfactory method of managing recurrences after irradiation in these areas. However, it has been demonstrated that voice and swallowing functions can be satisfactorily restored.

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* In Case VI recurrence in the base of tongue but not in larynx developed one year after surgical resection of the recurrence.

RESULTS OF INTENSIVE REGIONAL RADIATION THERAPY IN THE TREATMENT OF HODGKIN'S DISEASE AND THE MALIGNANT LYMPHOMAS OF THE HEAD AND NECK*

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DURING the past several years, interest in Hodgkin's disease and the malignant lymphomas has centered on the over-all results of intensive regional radiation therapy for localized disease.[1,2,3,8,9] Current interest, stimulated by Peters and Middlemiss' data on prophylactic irradiation,[9] is focused on the possibility of improving the results of definitive radiation therapy in both localized and early generalized disease, by routinely irradiating the surrounding uninvolved areas.[7]

Although fairly general agreement has been reached as to dosages required for permanent control of local manifestations of disease, comparatively little attention has been paid to the individual results of treatment of the 3 major regions, the head and neck, the mediastinum, and the abdomen, from the standpoint of extent and location of disease in relation to treatment techniques.[3,5] Nevertheless, a continuous endeavor to correct faulty techniques, a fundamental cause of local failure, is basic to progressive improvement in the radiotherapeutic results of treatment of the lymphomatous diseases. For example, an analysis of our results of treatment of Hodgkin's disease, lymphosarcoma, and nodular (follicular) lymphoma originating in the abdomen, revealed a substantial improvement following a change in treatment policy.[4] In reviewing our material on Hodgkin's disease and the malignant lymphomas clinically localized to the head and neck, emphasis has been placed on the relation of the results of treatment to histology, location and extent of disease, radiation therapy techniques, and tumor dose.

MATERIAL

Sixty-three cases of Hodgkin's disease and the malignant lymphomas clinically limited to the head and neck region, which were admitted prior to January 1, 1959, have been reviewed through December, 1965. A histologic diagnosis of Hodgkin's disease, clinically limited to the cervical lymph nodes, was established in 18 cases.

Of the malignant lymphomas, 26 were classed as lymphosarcoma (lymphocytic and lymphoblastic malignant lymphoma), 16 as reticulum cell sarcoma, and 3 as nodular (follicular) lymphoma. Because of the tendency for nodular lymphoma and lymphosarcoma to progress to the more malignant forms of lymphosarcoma and reticulum cell sarcoma respectively, the exact classification was somewhat arbitrary in a few cases with mixed cellular pattern and in those patients in whom the biopsy was necessarily small, *e.g.*, from Waldeyer's ring, *i.e.*, the nasopharynx, tongue, or tonsil.[6]

In contrast to Hodgkin's disease, which was limited to the cervical lymph nodes, the incidence of extra-lymph-node disease, with or without cervical lymph node involvement, was appreciable in the malignant lymphoma group. The incidence of lymphosarcoma clinically limited to extra-lymph-node sites was as follows: Waldeyer's ring 4, orbit 2, floor of mouth 1, and thyroid gland 1. In an additional 8 patients with involvement of Waldeyer's

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TABLE I

LOCATION OF INVOLVEMENT IN HODGKIN'S DISEASE AND THE MALIGNANT LYMPHOMAS CLINICALLY LOCALIZED TO THE HEAD AND NECK

(63 Patients Admitted through 1958—Analyzed through 1965)

Disease	No. of Patients	Cervical Lymph Nodes	Waldeyer's Ring	Waldeyer's Ring and Cervical Lymph Nodes	Extra-lymph-node Sites	Extra-lymph-node Sites with Cervical Lymph Nodes
Hodgkin's Disease	18	18	—	—	—	—
Lymphosarcoma	26	8	4	8	Floor of mouth 1 Orbit 2 Mental foramen 1 Thyroid 1	Orbit 1
Reticulum Cell Sarcoma	16	4	2	9	Antrum 1	—
Nodular Lymphoma	3	3	—	—	—	—

ring, the cervical lymph nodes were also affected. One of these patients, a white boy aged 13 years, whose disease included the nasopharynx, presented with a continuous sheet of tumor covering the nasal passages, the upper alveolar ridge together with the hard and soft palate. One patient with lymphosarcoma of the orbit had an enlarged ipsilateral upper cervical lymph node. In 8 patients, the disease was limited to the cervical lymph nodes. In 1 patient, the lymphosarcoma originated in a lymph node overlying the mental foramen of the mandible (Table I).

In the reticulum cell sarcoma group of 16 patients, the disease was clinically limited to the antrum in 1 and to Waldeyer's ring in 2. In an additional 9 patients with involvement of Waldeyer's ring, the cervical lymph nodes were also affected. In 4 patients, the cervical lymph nodes were solely involved.

In 3 patients with nodular lymphoma, the disease was limited to the cervical lymph nodes.

The age and race distribution was markedly different for the three major groups. In Hodgkin's disease, 61 per cent of the cases occurred in patients under 40 years of age, whereas in lymphosarcoma the incidence for the same age group was 35 per cent. Reticulum cell sarcoma did not occur in patients under 40 years (Table II). Because of the small number of cases in each group, the sex distribution is not statistically significant. However, the fact that 6 of 9 Negro patients presented with reticulum cell sarcoma may have significance.

CLINICAL FEATURES

HODGKIN'S DISEASE

Of the 18 patients with Hodgkin's disease, the involvement was limited to one side of the neck in 15. In 11 of these patients, the disease was situated sufficiently low to involve the supraclavicular fossa. One or both supraclavicular fossae were involved in the 3 patients with bilateral disease. The extent of disease, classed as limited, moderate, or extensive, was evenly distributed in both groups. However, 4 of 5 patients with minimal unilateral involvement were in the younger age group.

LYMPHOSARCOMA

A discussion of the clinical features of lymphosarcoma of the head and neck, which may have prognostic significance, is

TABLE II

COMPARATIVE AGE INCIDENCE ON ADMISSION OF PATIENTS WITH HODGKIN'S DISEASE AND THE MALIGNANT LYMPHOMAS

(63 Patients Admitted through 1958—Analyzed through 1965)

Age (yr.)	Hodgkin's Disease (18)		Lymphosarcoma (26)		Reticulum Cell Sarcoma (16)		Nodular Lymphoma (3)	
40 or <	11	(61%)	9	(35%)	—		1	(33.3%)
40–60	6	(33%)	7	(27%)	11	(69%)	1	(33.3%)
60 or >	1	(6%)	10	(38%)	5	(31%)	1	(33.3%)
Totals	9 White males 8 White females 1 Negro female		11 White males 15 White females		7 White males 3 White females 4 Negro males 2 Negro females		1 White male 1 Negro male 1 Negro female	

more difficult because of both the diversity and complexity of the anatomic distribution. As in Hodgkin's disease, lymphosarcoma clinically limited to the cervical lymph nodes tended to be of limited extent in the younger age groups (3 of 4 patients were under 40 years of age), whereas the disease was more extensive in the older patients (4). Five of 8 patients had involvement of the supraclavicular fossa.

In all but 1 of 12 patients with involvement of Waldeyer's ring, the local disease was massive regardless of the age or status of the cervical lymph nodes. In general, the lymphomatous process had extended from the site of origin, *e.g.*, the tonsil to the surrounding pharyngeal structures. In 1 patient, the involvement included the nasopharynx, tonsils, base of tongue, pharyngeal walls, and the entire extrinsic larynx including the false vocal cords.

Although less obvious than in patients with disease limited to the cervical lymph nodes, lymphosarcoma involving the cervical lymph nodes in conjunction with Waldeyer's ring, tended to be more extensive in the older age group. Of 8 patients with Waldeyer's ring and cervical lymph node involvement, the supraclavicular fossa was clinically involved in 3.

Of the extra-lymph-node sites other than Waldeyer's ring, the orbit was the only structure involved in more than 1 patient. Orbital involvement occurred in 3 patients. Two of these patients were over 60 years of age. In 1 elderly patient, the disease was minimal. In the other 2 patients, the eye was proptosed as a result of massive invasion of the extra-ocular structures. One patient presented with concurrent enlargement of an ipsilateral upper cervical lymph node.

RETICULUM CELL SARCOMA

In the group of patients with reticulum cell sarcoma involving Waldeyer's ring, the disease tended to be somewhat less extensive than in the lymphosarcoma group with 1 exception of reticulum cell sarcoma involving the nasopharynx and antrum. However, associated involvement of the cervical lymph nodes was more frequent. Of 9 patients with concurrent involvement of Waldeyer's ring and cervical lymph nodes, the supraclavicular fossa was involved in 4. The extent of disease in 3 of 4 patients with reticulum cell sarcoma limited to the cervical lymph nodes was massive. One patient had involvement of the supraclavicular fossa.

NODULAR LYMPHOMA

Of 3 patients with nodular lymphoma, 1 was referred following a radical neck dis-

section in another hospital for treatment of residual disease. In 1 patient, with a mixed cell pattern of nodular lymphoma and reticulum cell sarcoma, the disease was limited to the left submaxillary fossa. One patient presented with a number of small lymph nodes in both sides of the neck.

TREATMENT

Our policy of treatment of Hodgkin's disease and the malignant lymphomas, clinically limited to the head and neck, has been to administer intensive irradiation to the entire region surrounding the area of palpable or visible disease. Prior to 1954, all patients were treated with the 250 kv. unit. Following the introduction of the cobalt 60 unit, the policy of treatment for Hodgkin's disease and the malignant lymphomas of the head and neck was gradually changed over a 4 year period in favor of megavoltage. Initially, because of the relatively poor tolerance of the mucous membranes of the oral and pharyngeal cavities for large volume kilovoltage irradiation, patients with involvement of Waldeyer's ring were preferentially selected for treatment on the cobalt 60 unit. However, a gradual routinization of the practice of administering prophylactic irradiation to the surrounding clinically uninvolved areas, not very practical with 250 kv. irradiation, resulted in the abandonment of kilovoltage for even unilateral disease in the neck.

TREATMENT OF DISEASE LIMITED TO THE NECK

Kilovoltage. Thirty-three patients were treated for Hodgkin's disease and the malignant lymphomas clinically limited to the neck. Twenty-six were treated with 250 kv. irradiation and 7 with cobalt 60. Of the 26 treated with kilovoltage, 14 were treated for Hodgkin's disease, 6 for lymphosarcoma, 4 for reticulum cell sarcoma, and 2 for nodular lymphoma. Treatment was directed to the entire side of the neck including the supraclavicular fossa. As a standard approach, the head was turned obliquely to expose the posterior cervical chain (Fig. 1). When indicated, definitive or prophylactic treatment to the opposite side of the neck and the mediastinum was given through separate fields.

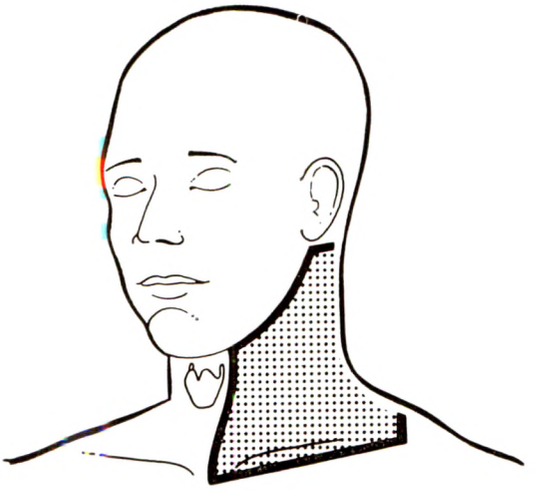


Fig. 1. 250 kv. field used for Hodgkin's disease or malignant lymphoma.

Because of the close proximity of the cervical lymph nodes to the skin, the dose to the neck is quoted as the given dose. Treatment was administered at a rate of 600 to 1,000 r per week. The total definitive dose delivered to the entire side of the neck ranged between 3,000 and 4,000 r. Residual disease was treated through reduced fields with doses of 500 to 1,500 r at a rate of 200 r per day. Prophylactic irradiation of the opposite neck was administered at the same rate as definitive treatment for a total of 1,000 to 3,000 r. A prophylactic dose of 2,000 to 2,500 r delivered to the midmediastinum through parallel opposing anterior and posterior fields was accomplished in 2 to 6 weeks.

Of 26 patients treated with 250 kv. irradiation for Hodgkin's disease and the malignant lymphomas clinically limited to the neck, 22 presented with unilateral involvement. Three patients with Hodgkin's disease and 1 with nodular lymphoma had bilateral disease. Of the 22 patients treated definitively for unilateral disease, 5 patients with Hodgkin's disease and 1 patient with lymphosarcoma received pro-

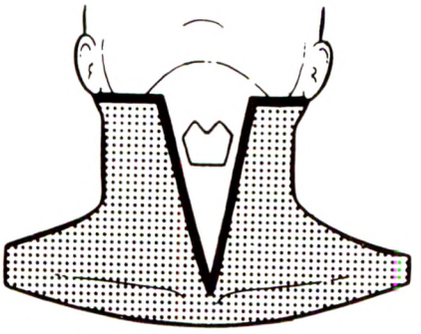


Fig. 2. Cobalt 60 field for Hodgkin's disease of the anterior neck. A posterior field (Fig. 3) should be added for clinical involvement of the posterior cervical chain to equalize the tumor dose throughout the neck.

phylactic irradiation to the opposite side of the neck. Prophylactic irradiation to the mediastinum was administered to 6 patients (4 with Hodgkin's disease and 2 with lymphosarcoma and reticulum cell sarcoma).

Despite the high incidence of involvement of Waldeyer's ring associated with malignant lymphoma of the upper cervical lymph nodes, prophylactic irradiation to Waldeyer's ring in conjunction with definitive treatment to the neck was not considered to be justified with kilovoltage irradiation because of the severity of the mucous membrane reaction.

Megavoltage. Of 7 patients treated with cobalt 60 irradiation for disease clinically limited to the cervical lymph nodes, 4 were diagnosed as cases of Hodgkin's disease, 2 as lymphosarcoma, and 1 as nodular lymphoma showing a transition to reticulum cell sarcoma.

The 4 patients with Hodgkin's disease had unilateral enlarged lymph nodes involving the supraclavicular fossa. In addition to delivering definitive treatment to the affected side of the neck, prophylactic irradiation was administered to the opposite neck in 3 and to the mediastinum in 4. Treatment was delivered to the neck through a single anterior or parallel opposing anterior and posterior fields (Fig. 2 and 3). In 3 patients, the anterior field covering the neck was extended to include the mediastinum (Fig. 4). Treatment to the neck was administered at a rate of 1,000 r per week for a total tumor dose of 3,000 to 4,000 r. Additional irradiation was given for residual disease. The prophylactic dose delivered to the midmediastinum was in the order of 2,000 to 2,500 r administered in 3 to 4 weeks.

In 3 patients treated with cobalt 60 irradiation for malignant lymphoma other than Hodgkin's disease, the upper neck was unilaterally involved in 2 (nodular lymphoma and lymphosarcoma). A few small lymph nodes were scattered throughout both necks in the third patient who presented with lymphosarcoma.

Since treatment was well tolerated, these patients received prophylactic irradiation to Waldeyer's ring in conjunction with definitive cobalt 60 irradiation to the neck and supraclavicular fossae (Fig. 5). Two patients with lymphosarcoma were given tumor doses of 4,000 r delivered in 4 weeks to Waldeyer's ring, both necks, and the supraclavicular fossae. One of these patients received concurrent prophylactic irradiation to the mediastinum. The third patient, with a mixed cell pattern of nodular lymphoma and reticulum cell sarcoma, received the same basic treatment. However, an additional dose of 3,000 r was required to effect regression of palpable disease in the submental area.

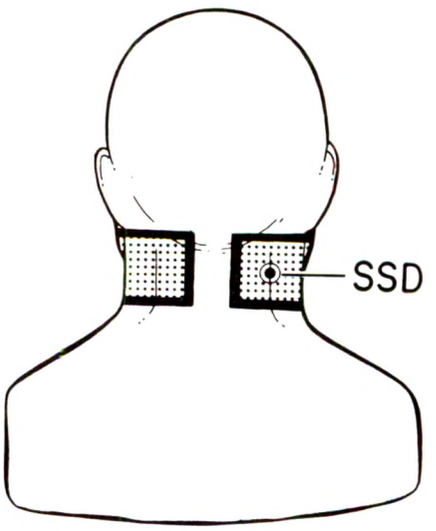


Fig. 3. Cobalt 60 posterior field for Hodgkin's disease of the neck (see legend of Fig. 2).

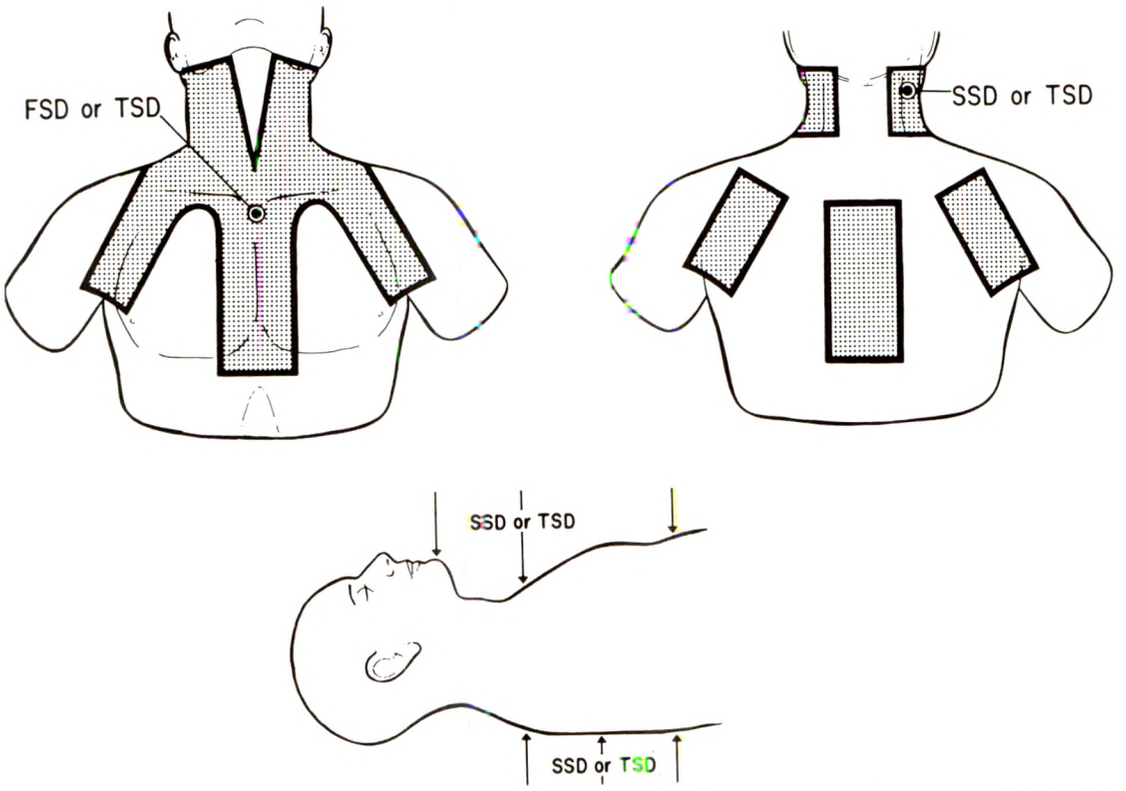


FIG. 4. Cobalt 60 "mantle" technique used for prophylactic irradiation of the mediastinum and the axillae in conjunction with definitive treatment of the neck.

TREATMENT OF WALDEYER'S RING

Kilovoltage. Because of the tendency for the malignant lymphomas originating in the nasopharynx, tonsil, or base of tongue to spread to the adjacent lymphatic tissues and to the lymph nodes of the neck, our policy of treatment has been to irradiate the entirety of Waldeyer's ring, the neck and the supraclavicular fossae, regardless of the extent of the primary lesion, or the clinical status of the neck (Fig. 5).

Treatment with 250 kv. irradiation was administered through parallel opposing lateral fields centered over Waldeyer's ring

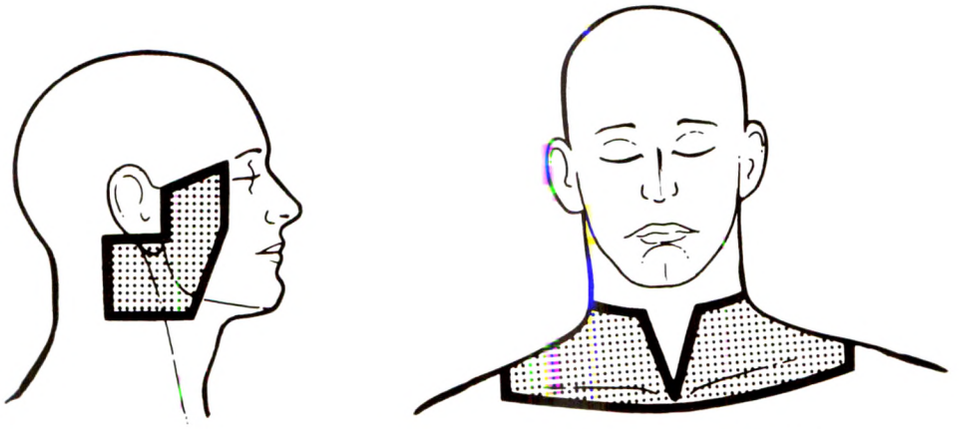


FIG. 5. Cobalt 60 fields designed to cover Waldeyer's ring, the neck, and the supraclavicular fossae.

and the upper neck. The supraclavicular fossae and the lower neck were treated through separate anterior fields. Because of the limited tolerance of the skin of the lateral fields, supplemental treatment to the primary lesion was administered through superimposed small lateral or anterior antral fields to achieve a tumor dose of close to 1,000 r per week for moderately sized lesions. Extremely massive tumors were treated at a somewhat slower rate. With 1 exception, the total tumor doses achieved were equally distributed between 3,000 and 5,000 r.

Treatment to the neck and the supraclavicular fossae was administered at a much slower rate. The dose to the supraclavicular fossae seldom exceeded 3,000 r delivered in 5 to 6 weeks. However, residual disease was given additional treatment through reduced fields. Of 15 patients with involvement of Waldeyer's ring, 9 (8 of whom had enlarged cervical lymph nodes) received treatment for reticulum cell sarcoma. Five of 6 treated for lymphosarcoma had involvement of the neck.

Megavoltage. In converting from 250 kv. to cobalt 60 irradiation, no change was made in the basic treatment fields covering Waldeyer's ring, the neck, or the supraclavicular fossae. However, the supplemental fields, used to boost the dose to the primary lesion with 250 kv. irradiation, were discontinued. Treatment was delivered at a rate of 1,000 r per week, not only to the primary site, but also to the neck and the supraclavicular fossae.

Eight patients with involvement of Waldeyer's ring were treated with cobalt 60 irradiation. Two patients with reticulum cell sarcoma, 1 of whom had enlarged cervical lymph nodes, received tumor doses of 4,500 r and 6,000 r. Five of 6 patients with lymphosarcoma were treated to doses of 4,000 and 4,500 r. Two of these patients had cervical lymph node involvement. One patient, the teen-aged boy who presented with a continuous sheet of tumor covering the nasal passages, palates, and nasopharynx was treated at a slower rate of 500 r per week to a total tumor dose of 3,000 r.

TREATMENT OF EXTRA-LYMPH-NODE SITES OTHER THAN WALDEYER'S RING

Treatment of malignant lymphoma originating from extra-lymph-node sites other than Waldeyer's ring was tailored to the individual lesion. For example, in 2 patients with massive orbital involvement the treatment encompassed the entire orbit, whereas in a third patient treatment was directed through a very restricted field to a small tumor situated at the junction of the palpebral and bulbar conjunctiva in the midline of the upper lid. In the first 2 patients, tumor doses of 2,500 and 4,000 r were delivered in 4 weeks through right-angled anterior and lateral fields using 250 kv. irradiation. Wedge filters were used to achieve a uniform isodose distribution throughout the volume of tissue irradiated. One of the patients received definitive treatment to the left neck for involvement of the upper cervical lymph node chain. The third patient, with minimal involvement, was treated with 2,000 r in 4 weeks through a single anterior 250 kv. field, the cornea and lens being shielded from the direct beam.

One patient with reticulum cell sarcoma of the right antrum was treated to a tumor dose of 4,000 r in 4 weeks with 250 kv., using a converging 3 field arrangement. Despite the fact that the only evidence of lymphosarcoma in another patient was an enlarged lymph node overlying the site of the mental foramen, cobalt 60 irradiation was directed to the right hemimandible because of clinical evidence of involvement of the mental nerve. This patient received a tumor dose of 3,000 r in 3 weeks. The only patient to receive prophylactic irradiation to the neck presented with a lymphosarcoma of the floor of the mouth. Treatment was directed to an anterior cobalt 60 field covering the oral cavity and both necks, the given dose being 3,500 r. Additional treatment was administered to a small lateral field directed to the floor of the mouth to raise the tumor dose to 3,500 r, the total treatment time being $4\frac{1}{2}$ weeks. Treatment for massive lymphosarcoma of the thyroid was administered through lat-

eral cobalt 60 fields to a tumor dose of 3,000 r in $4\frac{1}{2}$ weeks.

RESULTS

The results of intensive regional radiation therapy in 63 patients admitted through 1958 with a diagnosis of Hodgkin's disease or malignant lymphoma clinically limited to the head and neck have been calculated through 1965, using the Modified Life Method. The over-all 5 and 10 year survival figures are 46 and 35.5 per cent (Table III). Although the number of cases available is too small for a detailed analysis of each of the 3 major groups, the difference in the crude 5 year survival figures is striking, being 44 per cent for Hodgkin's disease, 58 per cent for lymphosarcoma, and 19 per cent for reticulum cell sarcoma (Table IV).

An analysis of duration of disease in relation to histology in 37 patients dead of Hodgkin's disease or malignant lymphoma further confirms the more aggressive behavior of reticulum cell sarcoma (Table V), as well as the rather benign course of nodular lymphoma. Of 14 patients deceased from reticulum cell sarcoma, 10 died within 1 year. In comparison, 5 of 10 patients with lymphosarcoma and 4 of 12 patients with Hodgkin's disease were deceased within the first year. Three patients developed generalized disease in the fifth, sixth, and tenth years, having been free of clinical evidence of tumor in the intervening years. One of these patients was originally treated for lymphosarcoma of the orbit. The other 2 were treated for Hodgkin's disease of the neck.

TABLE III

SURVIVAL CALCULATED ACCORDING TO THE MODIFIED LIFE METHOD* IN PATIENTS WITH HODGKIN'S DISEASE AND THE MALIGNANT LYMPHOMAS CLINICALLY LIMITED TO THE HEAD AND NECK

(63 Patients Admitted through 1958—Analyzed through 1965)

Years	Total No. of Patients	Survival (per cent)
1	63	79.4
2	50	63.5
3	40	54.0
4	34	47.6
5	30	46.0
6	29	44.4
7	28	41.2
8	25	41.2
9	20	41.2
10	17	35.5
11	10	31.1
12	5	24.2
13	3	24.2
14	2	8.1

* Berkson-Gage method.

TABLE IV

COMPARISON OF 5 YEAR RESULTS BY SPECIFIC HISTOLOGY

(63 Patients Admitted through 1958—Analyzed through 1965)

Histology	No. of Patients Alive in Relation to Total No. Treated	
Hodgkin's Disease	8/18	44%
Lymphosarcoma	15/26	58%
Reticulum Cell Sarcoma	3/16	19%
Nodular Lymphoma	3/3	100%

Regardless of histology, comparison of the surviving and deceased patients by age on admission revealed a totally different age distribution (Tables VI, VII, VIII) in that the surviving patients are in the younger age groups, whereas the majority of the deceased patients were in the older age groups. Supportive evidence that the malignant lymphomas and Hodgkin's disease are more aggressive in older patients is the fact that disease in the neck was more advanced in the older age groups.

Recurrences in the head and neck region have been reviewed by site of involvement (Table IX). Of 26 patients with disease clinically limited to the neck who were treated with 250 kv. irradiation with doses of 3,000 to 4,000 r delivered at an average rate of 750 r per week, 8 developed a local recurrence (Hodgkin's disease 4, lymphosarcoma 1, reticulum cell sarcoma 3). Two additional patients treated with 250 kv. irradiation for reticulum cell sarcoma of Waldeyer's ring and the associated cervical lymph nodes developed a local recurrence limited to the neck.

TABLE V

RELATION OF HISTOLOGY TO DURATION OF DISEASE IN 42 DECEASED PATIENTS (5 OF INTERCURRENT DISEASE)

	1 Yr.	2 Yr.	3 Yr.	4 Yr.	5 Yr.	6 Yr.	10 Yr.	11 Yr.	14 Yr.	Total
Hodgkin's Disease										
Dead of disease	4	4	1	—	2	1	—	—	—	12
Dead of intercurrent disease	—	—	—	—	—	—	—	—	—	—
Lymphosarcoma										
Dead of disease	5†	2	1	1†	—	—	1	—	—	10
Dead of intercurrent disease	1	—	1	—	—	—	1	1	—	4
Reticulum Cell Sarcoma										
Dead of disease	10	2	1	—	—	1	—	—	—	14
Dead of intercurrent disease	—	—	—	—	—	—	—	—	—	—
Nodular Lymphoma										
Dead of disease	—	—	—	—	—	—	—	—	1*	1
Dead of intercurrent disease	—	—	—	—	—	—	—	1	—	1
Total										
Dead of Hodgkin's disease or malignant lymphoma	19	8	3	1	2	2	1	—	1	37
Dead of intercurrent disease	1	—	1	—	—	—	1	2	—	5

* Patient with generalized disease in good general health—killed in automobile accident.
† Two patients with lymphosarcoma died as a result of recurrence in local site at 1 and 4 years.

Recurrence in Waldeyer's ring occurred in 3 patients treated for lymphosarcoma. One patient treated conventionally with 250 kv. irradiation to a tumor dose of 5,000 r in 6 weeks developed a recurrence in the base of the tongue and in the upper cervical lymph nodes bilaterally. A second patient, also treated conventionally but with cobalt 60 irradiation to a tumor dose of 4,000 r in $3\frac{1}{2}$ weeks for a lesion in the nasopharynx, developed a local recurrence in the fourth year. The third patient, the teen-

TABLE VI

RESULTS ACCORDING TO AGE DISTRIBUTION IN HODGKIN'S DISEASE OF THE HEAD AND NECK

(18 Admitted through 1958—Analyzed through 1965)

Age	Alive 6	Dead 12
<–10	0	1
11–20	1	2
21–30	4	2
31–40	0	1
41–50	0	1
51–60	1	4
61–70	0	0
71–80	0	1
	2 Males 4 Females	7 Males 5 Females

TABLE VII

RESULTS ACCORDING TO AGE DISTRIBUTION IN LYMPHOSARCOMA OF THE HEAD AND NECK

(26 Admitted through 1958—Analyzed through 1965)

Age	Alive 12	Dead 14	Dead of Intercurrent Disease 4
10–20	1	1	—
21–30	3	0	—
31–40	4	0	—
41–50	1	1	—
51–60	3	2	1
61–70	0	7	1
71–80	0	2	1
81–90	0	1	1
	6 Males 6 Females	5 Males 9 Females	2 Males 2 Females

age boy, presented with local recurrence in the nasal passages *et cetera* at 1 year.

Of 7 patients treated for disease originating in extra-lymph-node sites, only 1 developed a local recurrence. This patient was treated with cobalt 60 irradiation for lymphosarcoma of the thyroid.

Of the entire group of 14 patients who developed a local recurrence, 13 are deceased. Retreatment for control of local recurrence was ineffectual in the few patients in whom it was attempted.

Of 13 patients who received prophylactic irradiation to the midmediastinum, only 2 of 9 patients with Hodgkin's disease developed a local recurrence. Three patients treated for lymphosarcoma and nodular lymphoma localized to the upper neck received prophylactic irradiation to Waldeyer's ring in conjunction with definitive cobalt 60 irradiation to the neck. None of these patients developed clinical evidence of malignant lymphoma in Waldeyer's ring. One patient, with lymphosarcoma localized to Waldeyer's ring, developed new disease in the neck together with recurrence in the nasopharynx despite a prophylactic dose of irradiation of 4,000 r in 4 weeks.

Table VIII

RESULTS ACCORDING TO AGE DISTRIBUTION IN RETICULUM CELL SARCOMA OF THE HEAD AND NECK
(16 Admitted through 1958—Analyzed through 1965)

Age	Alive 2	Dead 14
10–20	—	—
21–30	—	—
31–40	—	—
41–50	2	2
51–60	—	7
61–70	—	2
71–80	—	3

Complications of intensive irradiation for Hodgkin's disease and the malignant lymphomas of the head and neck were rare. As expected, 2 patients treated for massive orbital disease developed a cataract in the third year. Only 1 patient, who re-

Table IX

INCIDENCE OF LOCAL RECURRENCE IN RELATION TO HISTOLOGY AND TREATMENT

	Hodgkin's Disease		Lymphosarcoma		Reticulum Cell Sarcoma	
	250 kv.	Co^{60}	250 kv.	Co^{60}	250 kv.	Co^{60}
Neck						
Hodgkin's Disease 18	4/14		1/6		3/4	
Lymphosarcoma 8						
Reticulum Cell Sarcoma 4						
Waldeyer's Ring						
Hodgkin's Disease –				1/3		
Lymphosarcoma 4						
Reticulum Cell Sarcoma 2						
Waldeyer's Ring and Neck						
Hodgkin's Disease –						
Lymphosarcoma 8			1/5	1/3	2/8	
Reticulum Cell Sarcoma 9						
Extra-lymph-node Sites Other than Waldeyer's Ring						
Hodgkin's Disease –						
Lymphosarcoma 6				1/3*		
Reticulum Cell Sarcoma 1						

* Local recurrence in thyroid.

ceived 3,000 r over the thyroid area, developed myxedema.

Radiation therapy for new areas of involvement was not indicated in patients with acute forms of the lymphomatous diseases who died within the first 2 years of extremely generalized disease. Of 5 patients with chronic disease who received semiradical to radical abdominal radiation therapy, 2 died of generalized Hodgkin's disease at 1 and 3 years following treatment to the abdomen. Of 3 surviving patients, 2 received intensive abdominal irradiation in the third and fifth years for lymphosarcoma and Hodgkin's disease. The second patient had previously received prophylactic irradiation to the mediastinum. Both patients are alive and well 4 and 5 years post abdominal therapy, making a total survival time of 7 and 9 years. The third patient, treated for Hodgkin's disease in the right neck, developed generalized involvement in the ninth year, manifested by a mediastinal mass, a progressive infiltration in the left upper lung field, and enlarged cervical lymph nodes, more prominent on the previously unirradiated left side. Treatment consisted of intensive radiation therapy to the left neck and mediastinum, followed by a course of oral cytoxan. In the ensuing months, the infiltration in the lung gradually disappeared, together with the lymph node involvement in the right neck. However, the patient developed a mass in the pelvis which was treated with intensive irradiation followed 9 months later by intensive treatment to the upper abdomen for symptomatic disease. This patient is surviving clinically free of disease at 1 year following treatment to the upper abdomen.

DISCUSSION

Our 5 and 10 year results, 46 and 35.5 per cent, for intensive regional radiation therapy of Hodgkin's disease and the malignant lymphomas clinically limited to the head and neck were obtained in patients admitted during the years 1949 through 1958. The majority of these patients were treated with the 250 kv. unit. Although the doses administered were radical in relation to skin tolerance, an analysis of the incidence of local recurrences (Table IX) demonstrates that doses of 3,000 to 3,500 r delivered in 4 to 5 weeks were not adequate for reticulum cell sarcoma, or for moderately advanced manifestations of Hodgkin's disease and lymphosarcoma.[11]

Two hundred and fifty kilovolt irradiation has no place in the modern concept of intensive regional radiation therapy administered in combination with aggressive prophylactic treatment of the surrounding clinically uninvolved areas. Since converting from 250 kv. to cobalt 60 irradiation, our policy has been to administer a basic tumor dose of 4,000 rads in 4 weeks, giving additional treatment to residual disease, for Hodgkin's disease, lymphosarcoma, and nodular lymphoma. Reticulum cell sarcomas, being more resistant, have required tumor doses of 5,000 to 6,000 rads delivered at a rate of 1,000 rads per week.

Although the value of prophylactic irradiation has not been established beyond doubt, the evidence accumulated to date, strongly suggests that prophylactic irradiation, administered in conjunction with definitive treatment for localized disease will improve the over-all survival rate. Based on the high incidence of involvement of the supraclavicular fossae in patients with Hodgkin's disease or malignant lymphoma of the lower neck (27 of 47 patients) and on the frequency of mediastinal involvement occurring as a second manifestation of disease,[10] our policy, since converting to cobalt 60 irradiation, has been to administer a prophylactic dose of 2,500 to 3,000 rads to the midmediastinum (including more recently the axillae) in conjunction with definitive treatment to the neck (Fig. 4). Similarly, our policy as previously explained, has been to administer prophylactic irradiation to Waldeyer's ring in conjunction with definitive treatment to the neck in patients presenting with malignant lymphoma of the upper neck (Fig. 5).

The availability of lower extremity lymphangiography as a routine diagnostic pro-

cedure has altered our approach to the over-all management of patients presenting with Hodgkin's disease or malignant lymphoma clinically limited to the head and neck region. Prior to lymphangiography, over 40 per cent of patients treated for clinically localized involvement of the head and neck developed generalized disease with clinical evidence of abdominal involvement in the immediate follow-up period. Treatment for abdominal disease, following the development of signs or symptoms, seldom proved worthwhile. In contrast to the inferior results obtained with radiation therapy following the development of gross abdominal involvement, our experience has been that intensive large volume radiation therapy, administered routinely for abdominal involvement demonstrated by lymphangiography, will result in 2 or more years of clinical freedom from Hodgkin's disease or malignant lymphoma in a fair percentage of patients.

SUMMARY

The results of intensive regional radiation therapy for Hodgkin's disease and the malignant lymphomas clinically limited to the head and neck regions have been reviewed in 63 patients admitted prior to January 1, 1959. The 5 and 10 year survival figures for the entire group are 46 and 35.5 per cent.

The radiation therapy approach to the treatment of involvement of the head and neck has been considered from the standpoint of location and extent of disease, radiation therapy techniques, tumor dose, and total treatment time. Prognosis has been discussed in terms of histology, age, and extent of local involvement.

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THE VALUE OF 2 MV. ROENTGEN-RAY THERAPY IN DIFFERENTIATED THYROID CARCINOMA*

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THERE continues to be a great diversity of opinion regarding the proper choice of therapy for the patient with thyroid carcinoma. It has been supposed that surgery is the best definitive method of treatment. Other therapeutic measures such as external irradiation, radioiodine, chemotherapy, and drug suppression (TSH hormone manipulation) usually have been used either as adjuncts to definitive surgery or in inoperable cases. It is often difficult, therefore, to determine the true value of an individual mode of treatment since it is seldom used alone. In this clinic, there are no reported results in patients treated only with surgery. Furthermore, the biologic behavior of thyroid cancer in itself may be quite variable so as to provide further difficulties in assessing treatment results.

In a previous report[15] we presented the results of 2 mv. roentgen-ray therapy in the treatment of inoperable undifferentiated thyroid carcinoma. Although the results were not spectacular, definite variants and differences in radiosensitivity were found. The present paper deals with a similar evaluation of the results of 2 mv. radiation in the treatment of differentiated thyroid carcinoma. It is hoped that the study may assist in the total evaluation of the role of external irradiation in the management of thyroid cancer.

MATERIALS AND METHODS

Fifty-nine patients with differentiated (papillary or follicular) carcinoma of the thyroid were treated by conservative, nondefinitive surgery followed by 2 mv. radiation. Although the preferred method of therapy in our group is to perform radical surgery, if feasible, the patients in this series did not receive such surgical treatment for various reasons to be elaborated upon later. The group of 59 patients represents approximately 25 per cent of all patients with thyroid carcinoma who were treated postoperatively with 2 mv. radiation between 1949 and 1960.

The microscopic slides on all 59 patients were reviewed together with the gross descriptions made at the time of accession. The following items were particularly noted: percentage of papillary and follicular components, nature of the stroma, blood vessel invasion, psammoma bodies, extension beyond gland capsule, multiple foci of tumor within the gland, and metastasis in lymph nodes. The uninvolved gland was studied to determine whether it was microscopically normal or showed changes such as adenomatous goiter or thyroiditis.

HISTOLOGY

Since the material available for pathologic study in this series often represented only a biopsy of the lesion, complete data regarding all tumors were not available. It was possible, however, to classify each tumor according to the percentage of papillary and follicular elements. Only 8 of the tumors were purely follicular. Fifty-one tumors showed papillary components which varied from minimal to pure papillary (1 case); the majority showed papillary formation in over 50 per cent of the tumor. Five of the 8 follicular tumors and nearly one-half of the papillary tumors showed blood vessel invasion. Psammoma

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bodies were never found in purely follicular tumors but were present in one-half of the papillary carcinomas. Extension beyond the gland and multiple foci of tumor within the gland were found in about one-half of both papillary and follicular cases. The uninvolved thyroid was available for study in 41 cases; 10 showed adenomatous goiter, 15 showed chronic thyroiditis, 1 showed primary hyperplasia (Graves' disease), and 15 were normal.

STAGING

Table 1 shows our present concepts of staging thyroid carcinoma. Although staging is of value in many cancers for prognostic purposes, an important purpose is to form categories of cases which can be compared with one another. In both instances it is most important that lines of demarcation between stages (categories) be sharply drawn and recognizable; hence, ours is a combination of clinical and pathologic information.

The disease was confined to the gland without evidence of lymph node extension or gross invasion outside of the gland in 17 cases. In 6, the cancer was confined to one lobe (Stage IA). Eleven patients had involvement bilaterally or in the isthmus (Stage IB). We have placed isthmic involvement in Stage IB because of its potential to metastasize to either or both sides. From this series, evidence does not suggest that the substaging is prognostically significant since one patient from each of Stage IA and IB cases died from pulmonary metastases. This would not necessarily be true, however, for other histologic types of thyroid carcinoma.

As in other cancers, we have placed tumors with lymph node involvement in Stage II. This stage was further subdivided into IIA and IIB, first according to whether lymph node involvement was unilateral or bilateral respectively. If the superior mediastinum contained discrete lymph node disease, the staging of malignancy was advanced to Stage IIB. An isthmic lesion with central lymph nodes was also placed in Stage IIB, because previous concepts of dissemination would necessitate bilateral neck dissection as the surgical alternative. All 8 cases of Stage II disease were classified in Stage IIB.

Table 1

SURGICAL AND PATHOLOGIC STAGING IN THYROID CARCINOMA

Stage I
A—Confined to one lobe
B—Bilateral, multicentric, or in isthmus
Stage II—Primary as in Stage IA or Stage IB
A—Unilateral lymph nodes
B—Bilateral lymph nodes, lymph nodes in mediastinum, or midline lymph nodes
Stage III
Invasion of other tissues or structures in neck or adjacent mediastinum with or without lymph nodes
Stage IV
Distant metastases

Stage III includes patients with invasion of contiguous tissues and structures outside of the thyroid gland whether or not lymph nodes are involved. We have found in the past that recurrence in the neck tissues following previous surgery or invasion from a secondary process constitutes a more serious problem than cancer confined to the gland or to discrete lymph nodes. Thirty-two patients were in this category. Two patients had Stage IV disease; both had pulmonary metastases.

TREATMENT

Stage I. Six cases of unilateral disease were not suspected at operation; since gross disease was not apparent, roentgen-ray therapy in lieu of a second surgical procedure was the treatment elected.

Eleven patients with either bilateral disease or disease of the isthmus with or without another focus also were given roentgen-ray treatment in lieu of a second surgical procedure; according to surgical concepts bilateral neck dissection would be required in such cases. Six of these bilateral tumors were not suspected at operation and

TABLE II

STAGE IA

6 Cases

Case, Age, and Sex	Surgical Procedure	Survival*	Cause of Death
1 78 F	Bilateral subtotal thyroidectomy for hyperthyroidism	12 months (deceased)	Pulmonary metastasis
2 53 F	Bilateral subtotal	12 years (deceased)	Cardiac failure
3 30 F	Bilateral subtotal	11½ years; alive and well	
4 47 F	Left lobectomy	9 years; alive and well	
5 55 F	Left subtotal	7½ years; alive and well	
6 65 F	Excision of nodule in upper pole of right lobe; exploration for parathyroid tumor	6 years (deceased)	Carcinoma of colon

* Mean survival—10 years.

subtotal thyroidectomy was carried out.

Stage II. There were no Stage IIA cases in this series—in such cases unilateral neck dissection would have been performed. Stage IIA cases usually constitute the greatest number of cases and have been reported before in the general group of patients with thyroid carcinomas treated surgically and given 2 mv. radiation postoperatively.[6]

Eight cases were classified in Stage IIB—metastatic disease in both sides of the neck or lesions in the isthmus and in the neck or combinations of isthmus and lobe lesions with involved lymph nodes. Total thyroidectomy was the most radical operation performed except in 1 case in which a mediastinotomy was done to effect total thyroidectomy and this in the presence of massive lymphadenopathy which was excised.

Stage III. There are 32 patients in this group and of these only 3 had total thyroidectomy. In 2 of these 3, residual tumor was left on the trachea. Six of the 32 patients required tracheostomy at the time of surgery. Four had biopsies only, 2 of which were endotracheal biopsies. In all cases, the surgical note stated that excision was incomplete or resection was not possible.

Stage IV. Two patients are included; both received local roentgen-ray therapy in the presence of pulmonary metastasis. They will be discussed later.

All 59 patients received 4,800 to 5,000 r tissue dose, usually in 6 weeks. The treatment fields included the superior mediastinum, the entire cervical area, and the adjacent supraclavicular region within the confines of the coracoid processes as lateral landmarks. The superior mediastinum, as we determine it on portal roentgenograms, has its inferior margin at the level of the carina.

Field shaping was done to exclude the lung apices from the mediastinal irradiation. The spinal cord dose was approximately 50 per cent of the calculated tumor dose. It was reduced by the interposition of a lead rod suitably curved to fit the cervical spine curvature, and rotating synchronously with the patient.[16,17]

RESULTS

Stage IA. The mean survival time was 10 years in 6 cases in Stage IA (Table II). One death from pulmonary metastasis occurred

1 year after diagnosis and treatment. A second death occurred at 6 years as a result of metastasis from a carcinoma of the colon, and a third death occurred at 12 years from cardiac failure. Evidence of thyroid carcinoma was not found in either of these last 2 cases.

Stage IB. The mean survival time was 11½ years in 11 cases in Stage IB (Table III). In 1 case pulmonary metastasis appeared 10 years after treatment and the patient died 6 months later. A second death occurred 10½ years after treatment. The cause of death was metastasis from carcinoma of the colon; there was no evidence of thyroid carcinoma. This group includes 1 of the 2 patients in this series lost to follow-up. This case was lost after 5½ years. The 5 year survival for the 17 patients classified in Stage I, therefore, is 94 per cent.

Stage IIB. Table IV shows 8 cases classified in Stage IIB. All patients were alive 5 years after treatment, and the length of survival ranged from 5½ to 14 years. One patient died at 6½ years from an unrelated brain tumor. One case is considered a failure of roentgen-ray therapy; 4 years, 9 months after treatment the carcinoma recurred in

TABLE III

STAGE IB

11 Cases

Case, Age, and Sex	Surgical Procedure	Survival*	Cause of Death
7 51 F	Resection of isthmus; subtotal lobectomy, left	15½ years; alive and well	
8 49 F	Bilateral subtotal	14 years; alive and well	
9 32 F	Bilateral subtotal	12½ years; alive and well	
10 50 F	Bilateral subtotal (isthmus)	12 years; alive and well	
11 24 F	Total	12 years; alive and well	
12 18 F	Bilateral subtotal	11½ years; alive and well	
13 46 M	Bilateral subtotal	11½ years; alive and well	
14 53 F	Total	10½ years; deceased	Pulmonary metastasis appeared at 10 years
15 66 M	Bilateral subtotal	10½ years; deceased	Carcinoma of colon; no evidence of thyroid carcinoma
16 48 F	Bilateral subtotal	6½ years; alive and well	
17 35 F	Bilateral subtotal (isthmus)	5½ years; alive and well†	

* Mean survival—11½ years.
† Lost to follow-up after 5½ years.

TABLE IV

STAGE IIB

100 PER CENT 5 YEAR SURVIVAL

Case, Age, and Sex	Primary Lesion	Cervical Lymph Nodes	Mediastinal Lymph Nodes	Isthmus Lesion with Lymph Nodes	Surgical Procedure	Survival
18 17 F	Bilateral	Bilateral	o	o	Subtotal with excision of lymph nodes	14 years; alive and well
19 45 F	Normal thyroid (FHL)	Bilateral	o	o	Excision of lymph nodes	12 years; alive and well
20 62 F	Right lobe and isthmus		o	+	Total	6½ years; alive and well; died of brain tumor
21 37 F	Isthmus lesion, 1954	o	o	+ with midline lymph nodes	Excision of isthmus and lymph nodes, 1954	Recurred in right lobe, 4 years 9 months
	Right lobe, 1958	o	o	o	Right lobectomy, Dec. 1958	12 years; alive and well
22 38 F	Isthmus lesion	Left cervical and midline	o	+with midline lymph nodes	Right total and left subtotal	11 years; alive and well
23 33 F	Bilateral	Right neck and mediastinal	Massive	o	Total with mediastinotomy	8 years; alive and well
24 14 F	Bilateral with nodule in isthmus	Right neck	o	+and both lobes	Total	6 years; alive and well
25 10 F	Left lobe and isthmus	+	o	+and left lobe and central lymph node	Resection of isthmus and left lobe	5½ years; alive and well

the right lobe. At the first operation, the isthmus had been resected and the midline lymph nodes excised. Following a right lobectomy, she has lived without disease another 7 years for a total of 12 years. The recurrence showed mixed papillary, follicular, and undifferentiated carcinoma.

The 5 year survival rate with conservative surgery and 2 mv. roentgen-ray therapy in these 8 cases is 100 per cent, but when radiotherapy is considered the means of control, the 1 failure described above lowers the survival rate to 88 per cent. This one failure in the solution of the local problem of Stages I and II thyroid carcinoma suggests that the surgical procedure of choice is a radical bilateral subtotal or total thyroidectomy. This would also leave the patient prepared for any eventual treatment with radioactive iodine.

Stage III. Of the entire series of 59 cases, 32 were classified in Stage III (Table V).

Group A. We divided the cases in Stage III into 2 groups. Group A, a clinical subgroup only, consists of 4 cases (Table VI), first classified in Stage III, in which the disease recurred. Three of these patients originally were given orthovoltage therapy and 1 received supervoltage therapy. All 4 had survived for long intervals when the disease recurred locally. In our survival study, we have used survival after treatment for recurrence and not total time since first treatment.

Case 28 had survived 6 years after the original treatment when recurrence was noted. A second course of 4,800 r with 2 mv. was given to a localized field. She died 15 months later; we were unable to learn the cause of death.

The second patient, Case 47, lived 8½ years before the disease recurred; he sur-

TABLE V

STAGE III

32 Cases

Case, Age, and Sex	Structures Invaded	Lymph Nodes	Surgical Procedure	Complications	Survival
26 62 M	Trachea; larynx; muscle	+	Left lobectomy; tracheostomy	Tracheo-esophageal fistula	Deceased; 4 months
27 15 M	Trachea; mediastinum	o	Bilateral subtotal; excision strap muscles	None	15½ years; alive and well
28* 57 F	Massive involvement of neck and mediastinum, not resectable (FHL)	+	Biopsy only	Marked tracheal irritation	Deceased; 7 years over-all; 15 months after treatment here
29 58 F	Trachea; diffuse in neck	o	Excision enough to allow tracheostomy	Developed persistent stoma, closed surgically	5 years; no thyroid carcinoma; died of breast carcinoma
30 61 F	Diffuse in left neck; fixed to muscles and jugular fat invasion	o	Bilateral subtotal	None	Deceased; 4 years 9 months; neck negative; cerebral hemorrhage
31 49 F	Trachea	+	Subtotal left; residual tumor	None	Alive and well, 13 years
32 74 F	Trachea with bleeding	+	Endotracheal biopsy	None	Deceased; 22 months; neck negative; coronary attack
33 62 M	Esophagus; carotid sheath; muscles	o	Biopsy; tracheostomy	Gastrostomy 6 months after treatment	Deceased; 10 months; neck improved; cerebral hemorrhage
34 51 F	Massive disease invaded dome of pleura and muscle	Massive mediastinal	Right partial lobectomy; isthmus	Right recurrent paralysis postoperatively	Alive and well, 12 years
35 37 M	Recurrent disease; local invasion	o	Total, second time	10 years after roentgen treatment; widespread metastasis	Deceased; 16 years from first operation; 10+ years after roentgen treatment
36 57 F	Trachea; muscle; right recurrent nerve	o	Right total with piece of trachea	Pulmonary metastasis in 15 months; no radioactive iodine	Deceased; 5½ years with pulmonary metastasis; neck negative
37 42 F	Muscle; multifocal disease	o	Bilateral subtotal	None	Alive and well, 12 years
38 49 M	Trachea	+	Total bilateral; strap muscles	None	Alive and well, 11½ years
39 19 M	Muscle; massive disease	+	Incomplete resection; partial lymph node excision only; tracheostomy	Postoperative tetany	Alive and well, 11 years
40 55 F	Massive mediastinal extension; not resectable	+	Partial lobectomy; excision of some lymph nodes; tracheostomy	Bone metastasis 7 years later; neck recurrent 9 years later	Alive with disease, 9½ years
41 43 M	Trachea	+	Right total; left subtotal; excision of lymph nodes	None	Alive and well, 9 years
42 60 F	Muscle; trachea; right recurrent nerve	o	Right total; left subtotal; excision strap muscles	Recurrent in lymph nodes 5½ years later; metastasis to lungs 6½ years later	Treatment with radioactive iodine; alive 9½ years
43 31 M	Carotid body; right recurrent nerve; muscle; right superior thyroid artery	+	Right total; tumor not resectable	None	Alive and well, 8½ years
44 21 M	Right recurrent nerve; mediastinum; trachea; muscle	o	Right total; tumor not resectable	None	Alive and well, 8 years
45 40 F	Left neck compartment	o	Total left	None	Alive and well, 7½ years
46 32 F	Mediastinum	+	Left total; partial excision right; not resectable	None	Last follow-up 4½ years; lost
47* 53 M	Recurrent tumor of larynx; previously treated case	+	Endolaryngeal biopsy	Tracheostomy for obstruction	Deceased; alive without disease 5½ years; cerebral hemorrhage
48 68 F	Trachea and esophagus	o	Partial excision; tracheostomy	Lung and pleural metastasis 3½ years later; improved with radioactive iodine; neck negative	Deceased; 4 years; coronary attack; had lymph node metastasis
49 51 F	Trachea; muscle	+	Total but tumor left on trachea	Breast carcinoma 4 years later	Alive and well, 7 years

* Recurrent case.

TABLE V (*Continued*)

Case, Age, and Sex	Structures Invaded	Lymph Nodes	Surgical Procedure	Complications	Survival
50 9 F	Trachea; bilateral disease; lymph nodes; isthmus	+	Almost bilateral total; tumor left on trachea	None	Alive and well, 7 years
51 46 F	Left recurrent nerve; jugular lymph node; adherent to trachea and esophagus	+	Excision jugular lymph node; partial excision; not resectable	None	Alive and well, 6 years
52 43 F	Second recurrence; mass growing out through strap muscles	o	Third operation; excision remnant	Pulmonary metastasis in 3 months; radioactive iodine	Alive with pulmonary metastasis 5½ years; neck negative
53* 67 F	Carotid; vagus; jugular in 1952	o	Biopsy; not resectable	Tracheal bleeding 8 years later; local recurrence and treatment again	Axillary metastasis; deceased, 6 months; local recurrence not relieved
54 63 F	Second recurrence; invasive recurrent lymph node	+	Partial excision	Carcinoma of sigmoid 7 years after roentgen treatment	Deceased from bowel carcinoma, 7½ years; no thyroid recurrence
55 68 F	Right recurrent nerve; tumor posterior to trachea	o	Partial excision; not resectable	Carcinoma of cervix at same time; bladder carcinoma 1 year later	Alive and well, 6 years
56 20 F	Muscle invasion; mediastinum; multifocal	+	Bilateral subtotal Mediastinal	None	Alive and well, 5+ years
57* 46 M	Neck diffusely	o	Partial resection 1934; not resectable 1957	Treated with 180 kv. roentgen rays, 3 series 1934–1935, total air dose 7,100 r; recurrence treatment with 2 mv. roentgen rays to 4,000 r tissue dose; masses grew during treatment	Survived 23 years; fatal carotid hemorrhage 2 months after 2 mv. roentgen therapy

vived another 5½ years after retreatment with 2 mv., giving 4,800 r to a full field. This patient died of a cerebral hemorrhage; there was no evidence of tumor.

The third patient, Case 53, was originally treated with 2 mv. radiation. The carcinoma recurred in the neck 8 years after treatment. A tissue dose of 4,500 r to a localized field failed to control the recurrence and she died 6 months later. The original disease involved the carotid artery, vagus nerve, and jugular vein. The recurrence caused tracheal hemorrhage. Biopsies in 1952 and 1960 showed a tumor that was 50 per cent papillary and 50 per cent follicular.

The fourth patient, Case 57, had survived for 23 years after a partial resection and roentgen-ray treatment with 180 kv. on 3 occasions in 1933 and 1934. Radon

TABLE VI

STAGE III—GROUP A

Repeated Roentgen Therapy—4 Cases

Case, Age, and Sex	Survival after Original Therapy	Survival after Recurrence Treated	Cause of Death
28 57 F	6 years (200 kv.)	15 months	Unknown
47 53 M	8½ years (200 kv).	5½ years	Cerebral hemorrhage
53 67 F	8 years (2 mv.)	6 months	Local recurrence persisted with tracheal hemorrhage
57 46 M	23 years (180 kv.)	2 months	Carotid hemorrhage

TABLE VII

STAGE III—GROUP B

No Radical Neck Dissection—28 Cases
(4,800 r Tissue Dose with 2 mv.
Roentgen Therapy)

	Total	Per Cent	Death from Thyroid Carcinoma	Death from Other Causes
Five year survival	24	86	2 or 7%	2 or 7%

Note: Two cases in Stage IIB and 1 case in Stage IB showed microscopic evidence of muscle invasion and could have been put in this group theoretically.

seed implantation was also performed in 1934 for persistent disease. The disease recurred in 1957 and the patient was given a tissue dose of 4,000 r with 2 mv. roentgen-rays without effect on the recurrence during the treatment period. He died of a carotid hemorrhage 2 months later. We do not know the type of the recurrent tumor.

Group B. The other 28 patients in Stage III had only 1 series of roentgen-ray treatment following conservative surgical procedures, as discussed previously. Table VII shows that 24 patients, or 86 per cent, survived 5 years. There were 2 deaths from thyroid carcinoma; 1 patient with a tracheo-esophageal fistula died 4 months after definitive treatment and the other patient died of lung metastasis and a coronary attack 4 years after diagnosis and treatment. Two patients died from vascular accidents 1 and 2 years after treatment.

Five additional deaths from pulmonary metastasis have occurred after the 5 year period—in 2 cases at $5\frac{1}{2}$ years and in 2 cases at $9\frac{1}{2}$ years. None of the 4 had local recurrence. The fifth patient died $16\frac{1}{2}$ years after treatment. Originally, this patient had a subtotal resection. Disease recurred 6 years later; total excision of the remnants was performed and 2 mv. roentgen-ray therapy was given. Ten years later the disease again recurred locally and massively with widespread skeletal and pulmonary metastasis. The mean survival period to date is $9\frac{1}{2}$ years in this group.

Stage IV. We have treated 2 patients classified in Stage IV (Table VIII). The first was a 9 year old girl with bilateral disease, cervical lymph node metastasis, invasion of the trachea, and pulmonary metastasis (Fig.). These fine pulmonary metastatic lesions are typical of those representing a relatively benign process and we elected to treat the neck because of the residual tumor. She is alive and clinically well 6 years later. Figures 2 and 3 show progres-

TABLE VIII

STAGE IV

2 Cases

Case, Age and Sex	Clinical and Surgical Findings	Lymph Nodes	Surgical Procedure	Follow-up Data
58 9 F	Tracheal invasion; pulmonary metastasis	Bilateral	Total bilateral excision of right lymph nodes; mass on left of trachea	Pulmonary lesions enlarged after 5 years; clinically in good health; neck negative at 6 years (now aged 15 years)
59 28 M	Huge mass involving neck and extending into mediastinum; pulmonary metastasis	Bilateral	Biopsy only; 50% papillary, 50% follicular	Palliative attempt to relieve local condition; survived only 6 months; incomplete follow-up; neck masses were regressing under therapy; patient returned to Iran and was not seen after completion of roentgen therapy

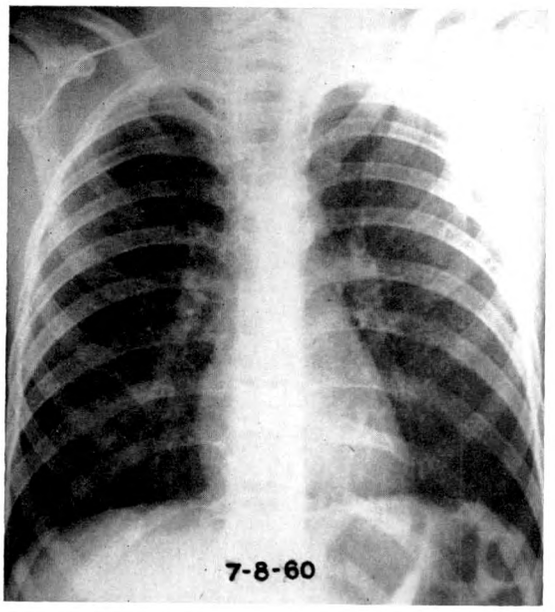


FIG. 1. Pulmonary metastasis in a 9 year old girl.

sion of the pulmonary lesions. The tumor in this case was 90 per cent papillary and 10 per cent follicular.

The second patient was a 28 year old foreign graduate student who had massive involvement of the neck and mediastinum and metastasis to several areas in the lungs. Biopsy revealed that the tumor was 50 per cent papillary and 50 per cent follicular. We treated him in an effort to relieve his local symptoms. Partial regression of neck masses was noted during the treatment period. He returned home and we learned that he died 6 months later.

DISCUSSION

Table IX is a summary of our end results in the 59 cases. Table X is a compilation of all deaths from thyroid carcinoma in this group of 59 cases. Of the 9 deaths from cancer, 4 of the patients had follicular carcinomas which often exhibit cells of the Hürthle cell type. In all 4, the tumor metastasized to the lung, and 2 of them were classified in Stage I. There were no other features in these 9 cases that would distinguish them from the remaining cases of the series. Our 5 year survival figures for papillary and follicular carcinoma of the thyroid are shown in Table XI and those from the literature are listed in Table XII. We realize that a 10 year follow-up will

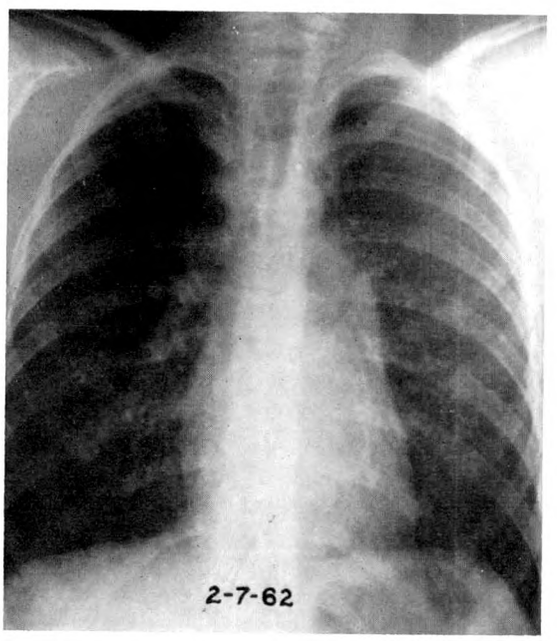


FIG. 2. Same patient as shown in Figure 1, one and a half years later.

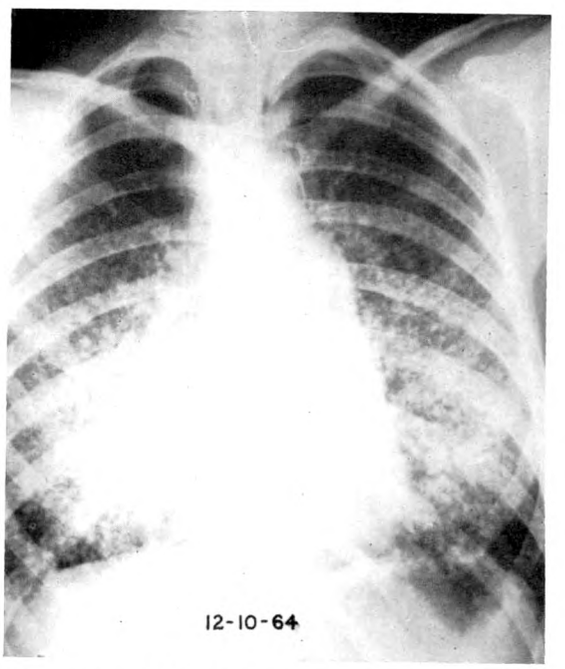


FIG. 3. Same patient as shown in Figures 1 and 2, four and a half years later.

be more informative because 6 of the 9 deaths in this group occurred from 5 to 10 years after definitive treatment.

The pathologic review of the tumors in this series is admittedly incomplete inasmuch as only biopsy material was available in many cases. From the material studied, however, it seems that the tumors were morphologically similar to papillary and follicular carcinomas in any unselected series. The incidence of vascular invasion, the presence of psammoma bodies, ex-

TABLE IX

SUMMARY OF END RESULTS

Stage	Total	Alive	Dead	Lost
IA	6	3	3	
IB	11	8	2	1
IIB	8	7	1	
III	32	18	13	1
IV	2	1	1	
Total	59	37	20*	2

* Only 9 patients died of thyroid disease.

TABLE X

SUMMARY OF 9 DEATHS DUE TO DIFFERENTIATED THYROID CARCINOMA

Case, Age, and Sex	Stage	Pathology	Course of Disease
1 78 F	IA	100% follicular	Pulmonary metastasis appeared in 9 months; deceased in 12 months
14 53 F	IB	100% follicular	Pulmonary metastasis 9½ years after roentgen therapy; neck negative; deceased in 10½ years
26 62 M	III	70% papillary, 30% follicular	Developed tracheo-esophageal fistula; died as a result of this complication in 4 months
28 57 F	III, recurrent	Papillary; not available for review	6 years after local excision only; tumor recurred; treated with 2 mv. roentgen rays and survived 15 months; cause of death unknown
36 57 F	III	100% follicular	Pulmonary metastasis seen in 15 months; patient lived total of 5½ years without specific therapy
48 68 F	III	80% papillary, 20% follicular	Pulmonary metastasis in 3½ years; treated with radioactive iodine, improved; deceased in 4 years with pleural metastases; had coronary attack; no recurrence in neck
53 67 F	III, recurrent	50% papillary, 50% follicular	Treated twice with 2 mv. roentgen rays; survived 8 years after first series; then recurred in trachea; second series, 4,500 r localized; had tracheal hemorrhage again; developed bilateral axillary lymph node involvement
35 37 M	III	100% follicular (Hürthle cell)	6 years from subtotal to recurrence; then total plus 2 mv. roentgen therapy; 10 more years before local recurrence second time of massive proportions in neck and widespread metastasis to skeleton and lungs
57 46 M	III, recurrent	40% papillary, 60% follicular	Partial resection; originally treated with 180 kv. roentgen rays 1934 and 1935 and with local radon implantation; recurred locally after 23 years; 4,000 r with 2 mv. not effective; fatal carotid hemorrhage in 2 months

TABLE XI

PAPILLARY AND FOLLICULAR CARCINOMA OF THE THYROID; 5 YEAR SURVIVAL

Treatment	No. of Cases	Per Cent
Radical surgery and orthovoltage roentgen therapy	62	60.0
Radical surgery and 2 mv. roentgen therapy	51	82.0
Conservative surgery and 2 mv. roentgen therapy	59	81.0

tension beyond the gland, and multifocal nature in this series were not considered to be different from those of an unselected group. It would appear that there are no characteristics inherent in the morphology of the tumors in this series that could clearly be identifiable as being useful in estimating response to therapy or prognosis.

The stage of the disease seems to be the important factor. In this relatively small group of 59 patients, 14 are alive with disease or succumbed to the disease, and of these, 10 are in Stage III and 2 in Stage IV.

Of concern to us is the matter of how to handle each stage. Presently, we are inclined to say that patients with Stage I tumors should have total or radical subtotal thyroidectomy. The guide to treatment should not be based on clinical staging alone. The sum of the knowledge of clinical, surgical, and pathologic findings should determine whether or not supplementary therapy is needed.

In Stage II tumors, the surgical procedure should be a very radical subtotal or

TABLE XII

FIVE YEAR SURVIVAL RATES FROM THE LITERATURE

Source	Papillary	Follicular	Mixed
Windeyer[16]			
20 cases—our Stage III (4,000 r min.)			55%
Jacobsson[8]			
A—Stages I and II			A—95%
B—Stage III			B—35%
Crile *et al.*[4]			
39 cases with conservative surgery—Stages I and II	87.3%		
McDermott *et al.*[11]			
Cumulative survival after surgery	73%	71%	
Martin[10]			
180 cases with radical surgery	62%		
Garland[5]			
42 cases with surgery, incomplete removal and orthovoltage therapy			47%
Brister *et al.*[2]			
Surgery alone—Stage I			52%
Roentgen therapy plus surgery—Stage II (beyond gland with or without lymph nodes)			
American Cancer Society[9] (not staged)			
203 papillary	61%		
105 follicular		54.2%	

total thyroidectomy with lymph node excision to determine the extent of disease. On occasion, this will effect excision of unknown primary growths elsewhere in the gland.

Our experience in supplementing surgery in the treatment of thyroid carcinoma has been in the use of external radiation. There is a growing literature of the use of radioactive iodine following limited surgical procedures, notably by Beierwaltes *et al.*,[1,7] and Rose and Kelsey[14] in this country and by Pochin[12] in England. The last mentioned assures us that papillary carcinoma of the thyroid can pick up iodine. In reviewing some of the literature on the use of I^{131}, we are left uncertain as to its actual value, largely because so little effort is made to stage and report on its effect on Stage III tumors. Much of the effort is clouded by the multiplicity of modalities used in any one case.

We feel, therefore, that we shall continue to use external radiation in any case in which there is known residual in the neck or in an obviously nonresectable situation.

Surgery in Stage III disease should be individualized. As much of the tumor as possible should be excised without compromising the blood supply to the area. This should be followed by external radiation.

The treatment of patients with Stage IV disease will remain largely palliative except in instances already shown and when radioactive iodine can be used with effect.

It may be that the infrequent occurrence of pure follicular carcinoma is important. There were 8 pure follicular carcinomas in this series of 59 cases. Of the 9 patients who died as a result of thyroid carcinoma, 4 had pure follicular tumors and 3 of them showed Hürthle cells.

SUMMARY

Papillary and follicular carcinoma of the thyroid is radiosensitive. The survival rate of 82 per cent for 5 years in surgically nonresectable cases using external radiation as the prime modality is equal to our results with radical surgery plus megavolt external radiation. The high 5 year survival rate in the limited number of cases in Stage I and Stage II suggests that radical surgery is not necessary.

The addition of external radiation should be reserved for cases in which surgery has not eradicated the known disease or in lieu of radical neck dissection when residual disease is known or suspected.

Our experience continues to show that better results are obtained with supervoltage than with orthovoltage radiation, primarily because we are able to deliver twice the dosage with fewer local reactions.

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SURGICAL TREATMENT OF CARCINOMA OF THE CERVIX, RECURRENT AFTER IRRADIATION OR COMBINATION OF IRRADIATION AND SURGERY*

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ON MORE than one occasion in the past, reports have been published from the Memorial Hospital for Cancer and Allied Diseases emphasizing the fact that recurrent carcinoma of the cervix following radiation therapy which at first seemed to effect a cure was amenable to surgical attack. Thus, the patient could be given a second chance for cure.

In this category are patients who have been treated by so-called "adequate" radiation therapy and in whom the lesion might have regressed for varying degrees but did not resorb to the point where upon pelvic examination it could have been considered as completely destroyed. Such cases are classified as persistent cancer. There have been various explanations for failure of irradiation. Among these are: (1) "inadequate dosage"—this is always difficult to define as some advanced lesions have been permanently controlled by "inadequte dosage"; (2) "poor technique"—again this is a matter of opinion even among experts; and (3) "radioresistance"—according to some radiation therapists this does not exist and always indicates faulty application of radiation.

Regardless of the polemics, the fact does remain that not an inconsequential number of patients is seen in a center who have had radiation therapy by specialists duly accredited as such by our present methods of certification and who either have not had complete regression of their cancers or who had a period of apparent cure followed by a return of the cancer in or around the site of the previous lesions.

The problem is what to do with these patients? Re-irradiation may be successful but this is not frequently observed. Local cauterizations with actual or electro-cautery may also be successful, but there are few patients who are suitable for such management.

On the Gynecological Service of the Memorial Hospital, 48 per cent of all cases of cancer of the cervix—ward and private patients admitted to the hospital or seen in the out-patient clinic—are problems of possible persistence or recurrence after treatment elsewhere. Excluded from this number are private patients seen by some of the staff members in their outside private offices who are not admitted to Memorial Hospital, but this total number is small and does not influence the results achieved in the larger series reported below.

MATERIAL AND RESULTS

A summary of 991 patients with the initial diagnosis of recurrent or persistent cervix cancer is shown in Table 1. Upon more detailed evaluation, 14 per cent (138 cases) did not actually have cancer. Of the 853 remaining patients in whom cancer was proven to be present, 443 or 52 per cent were subjected to surgery in an attempt to cure. In many of the untreatable cases, there was inordinately prolonged delay between appreciation of the recurrence and date of referral for surgical treatment. In-

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From Memorial Hospital for Cancer and Allied Diseases, New York, New York; and the James Ewing Hospital of the City of New York.
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TABLE I

MANAGEMENT OF PATIENTS PREVIOUSLY TREATED ELSEWHERE FOR CARCINOMA OF CERVIX
SEPTEMBER 1947–JANUARY 1960

Type of Management	No. of Patients	Living 5+ Years	Per Cent
Definitive surgery	443	106	23.9
Exploratory laparotomy (re-irradiation, 61)	153*	2†	
Palliative surgery (re-irradiation, 12)	86	0	
Re-irradiation only	56	3	
Refused treatment	40	4	
Consultation	10	2	
No treatment offered	65	1	
Definitive surgery for radiation necrosis	67	45	67.1
Successful treatment elsewhere (follow-up only)	42	30	71.4
Radiation complication (no cancer present)	29	21	72.0
Total	991	214	21.5

* One patient had exploratory laparotomy for bowel obstruction (no cancer), multiple fistulae—died 1 month later.
† One patient had nonresectable cancer treated by radiation—living and well at 6 years. One patient was explored 1 month after radiation therapy; clinically tumor involved bladder, rectum with walnut size nodule involving right psoas muscle and external iliac vessels. No positive biopsy obtained. Treated with radium and external radiation. Died 7 years later.

deed, such delays also existed among the treatable cases. This is not surprising in view of the widespread pessimism regarding the prognosis once radiation therapy has failed to cure the patient.

As with the surgical treatment in general, operation for cancer of the cervix must be chosen to fit each individual case depending upon the size of the lesion and the condition of the patient. The various types of operations performed on the 443 operated cases are summarized in Table II, showing incidence of 5 year survival without evidence of disease and the surgical mortality (death within 30 days).

One hundred and twenty-five patients had operations that were less than exenterations and thus normal urinary and fecal excretory functions were maintained. The 5 year survival among these was 50 patients or 40 per cent. The surgical mortality was 3 patients or 2.4 per cent—a small risk to pay for the second chance to survive.

There were 318 patients whose disease was so advanced that total or partial pelvic exenteration was necessary. Among these, 56 survived 5 or more years, an incidence of 17.6 per cent or half as great as when the lesion could be removed with less radical procedures. In the exenteration group, the surgical mortality was 54 patients (17 per cent). This elevated mortality is due to the fact that in the early days of the program palliation was attempted by exenterations performed leaving cancer behind against the pelvic walls. These cases had a high mortality and it soon became apparent that nothing could be achieved under such circumstances; therefore, such operations are no longer done. However, the cases cannot be excluded and their inclusion explains the elevated mortality figures. At present, total pelvic exenteration should not entail a higher than 5 to 10 per cent risk. The important point is that recurrent cervix cancer spread to the bladder and/or rectum can still be cured in at least about 1 out of 5 cases. By increasing the criteria for selection, much more substantial 5 year salvage results may be achieved, *i.e.*, in the order of 35 to 40 per cent.

CLASSIFICATION

The results related to previous types of treatment are shown in Table III. Classification of cases is according to the surgical and pathologic classification and the class

TABLE II

SURGICAL PROCEDURES USED IN THERAPY FOR PATIENTS WITH RECURRENT OR RESIDUAL CARCINOMA OF THE CERVIX
SEPTEMBER 1947–JANUARY 1960

Type of Surgery	No. of Patients	Living 5+ Years		Surgical Mortality	
		No.	Per Cent	No.	Per Cent
Total hysterectomy	2	1		1	
Wertheim hysterectomy*	7	1			
Schauta hysterectomy	1	0			
Hysterectomy and lymph node dissection†	75	30	40.0	1	
Stump and lymph node dissection	19	6	31.0	1	
Vaginectomy and segmental resection of sigmoid	1	0			
Vaginectomy and lymph node dissection	16	11	68.7		
Vaginectomy	1	1			
Lymph node excision	1	0			
Anterior exenteration	95	18	18.9	10	10.5
Total exenteration‡	217	37	17.0	44	20.0
Posterior exenteration	5	0			
Vulvectomy and excision of clitoris	1	0			
Anterior resection of rectosigmoid	1	0			
Hysterectomy, lymph node dissection and hemipelvectomy	1	1			
Total	443	106	23.9	57	12.8

* Includes 1 patient with partial resection of rectal wall; colostomy.
† Includes 1 patient with partial resection of rectal wall; colostomy.
‡ Includes 1 patient with hemipelvectomy.

TABLE III

RESULTS OF SURGERY IN PATIENTS WITH RECURRENT OR RESIDUAL CARCINOMA OF THE CERVIX ACCORDING TO SURGICAL AND PATHOLOGIC CLASSIFICATION AND PREVIOUS TREATMENT
SEPTEMBER 1947–JANUARY 1960

Pathologic Classification	Irradiation less than 6 mo. ago		Irradiation more than 6 mo. ago		Surgery		Surgery and Irradiation		Irradiation and Surgery		Total		
	No. of Patients	Living	No. of Patients	Living	No. of Patients	Living	No. of Patients	Living	No. of Patients	Living	No. of Patients	Living	Per Cent
O			3	2							3	2	
A	8	2	17	11			1	0			26	13	50.0
B	10	4	37	15	5	3	9	8			61	30	49.0
C	7	0	14	3	4	1	3	1	1	1	29	6	20.6
CN	2	0					1	1			3	1	
D	8	1	5	1			1	1	1	0	15	3	20.0
DC	3	0	11	1	2	0	5	1			21	2	9.5
E	18	4	61	16	11	5	21	5	3	1	114	31	27.2
EN	14	0	28	1	7	1	13	4	3	1	65	7	10.7
F	3	0	18	3	1	0	5	2	2	1	29	6	20.6
FN	8	0	22	2	3	0	11	1	8	0	52	3	5.7
Total	81	11 (14%)	216	55 (25%)	33	10 (30%)	70	24 (39%)	18	4 (22%)	418	104	24.8

This does not include 25 patients who had carcinoma discovered at subtotal hysterectomy; 2 are living and well 5+ years. (Five patients had anterior and 12 had total pelvic exenteration; 8 had stump excision and pelvic lymph node dissection.)

TABLE IV

SURGICAL SALVAGE OF IRRADIATION/SURGERY FAILURES IN CASES OF CARCINOMA OF THE CERVIX

	Truelsen (control series; no treatment of recurrences)	Memorial Hospital (surgical treatment for recurrences)
Failure of primary healing	390 cases—no survivors, 2 yr.	81 cases 14% 5 yr. survivors
Recurrence after primary healing	704 cases—3.5% alive with cancer at 5 yr.	216 cases 25% living, well 5 yr.
Recurrence after conservative surgery		33 cases 30% living, well 5 yr.
Recurrence after surgery and postoperative irradiation		70 cases 34% living, well 5 yr.
Recurrence after irradiation and surgery		18 cases 22% living, well 5 yr.
Total		418 cases 25% living, well 5 yr.

is determined only after pathologic study of the excised specimen. Here Class 0 refers to cases of epidermoid carcinoma confirmed by biopsy, but in which preoperative irradiation was given and the specimen showed no cancer. Other classes are defined as:

Class
- A Cancer limited to cervix
- B Cancer spread to fornices and/or lower uterine segment
- C Cancer in parametria
- CN Cancer in parametria with positive parametrial lymph nodes
- D Metastases in lymph nodes at periphery of pelvis
- DC Same as D with cancer in parametrium
- E Cancer invading bladder or rectum or both
- EN Same as E with positive pelvic lymph nodes
- F Cancer in musculature of pelvic floor with bladder and/or rectal invasion
- FN Same as F with positive lymph nodes

Furthermore, the cases are divided into groups depending upon the type of previous treatment received.

RESULTS ACCORDING TO PREVIOUS TREATMENT RECEIVED

PREVIOUS IRRADIATION LESS THAN 6 MONTHS AGO

In these patients, a full course of irradiation, usually with external ports, was given and following the treatment it became evident that the response was unsatisfactory. Therefore, they were rather promptly referred for surgery. Of a total of 81 patients, 11 (14 per cent) survived for 5 years. This group represents the more virulent forms of cancer and the low salvage rate is consistent with the principle that poor response to radiation augurs poor surgical results. The salvage rate approximates that obtained in patients having had gastric resection for cancer of the stomach. Poor as the results may seem, the situation still is not hopeless.

PREVIOUS IRRADIATION MORE THAN 6 MONTHS AGO

In this group, the salvage of 55 of 216 patients, *i.e.*, 25 per cent, includes patients whose initial response to radiation seems to have been better and there were apparent periods in which cure might have been achieved.

PREVIOUS SURGERY

The type of surgery carried out in this group had been relatively conservative, and when recurrences were noted they were referred for further surgical management. In 9 cases the surgery was indeed conser-

vative since the vaginal vault was preserved in 5 of them. In the other 4, cancer was present but limited to the parametria. Of the 9 cases, 4 (44 per cent) were 5 year cures. In the entire group of 30, 10 (33 per cent) survived for 5 or more years.

PREVIOUS SURGERY FOLLOWED BY IRRADIATION

Under these circumstances, proper radiation therapy could not be administered because of the excised uterus. The salvage rate was 24 among 70 patients, an incidence of 34 per cent.

PREVIOUS IRRADIATION THEN SURGERY

This small group represents patients with recurrent cancer after previous irradiation followed by surgery. The salvage rate among 18 cases was 4 patients, an incidence of 22 per cent. The irradiation consisted of a "full course" of therapy given preoperatively and then some relatively conservative form of hysterectomy.

The limited group of 25 patients who had received subtotal hysterectomy elsewhere and in whom cancer was discovered in the cervix at or after operation and who were then subjected to some inadequate form of radiation therapy or in whom expectant management was then carried out for a period yielded the poorest results. Only 2 survived 5 years, an incidence of 8 per cent. Seventeen had to have anterior or total pelvic exenteration and 8 had radical excision of the cervical stump and pelvic lymph node dissection.

THE VALUE OF LYMPHADENECTOMY

Comments by some authors in the literature indicate a pessimistic view concerning pelvic lymphadenectomy, especially after radiation therapy and in the presence of lymph node metastases.

In this study (Table III, Classes CN, D, DC, EN and FN), there were 98 cases of radiation failure with positive pelvic lymph nodes in the removed specimens; 6 (6 per cent) survived 5 years. Of 43 cases initially treated by surgery and irradiation in combination and whose specimens showed metastatic lymph nodes, there were 8 (18 per cent) 5 year survivors. In combining these two groups, out of 141 patients there were 14 (10 per cent) 5 year survivors. While such results are far from satisfactory, it is, nevertheless, evident that under such unfavorable circumstances the situation is not hopeless. Certainly, from the point of view of the patient's chances for survival and the attitude on the part of the clinician who should increasingly labor to salvage his patients, the conception of the futility of pelvic lymphadenectomy should not be condoned. Unfortunately, the question of ability to carry out satisfactory radical lymphadenectomies enters the picture and it is regrettable that there is more than a tendency to consider as futile what one cannot do properly himself. If adequate surgical talent is not available, it should be sought after and endeavors continued to facilitate adequate training opportunities if they do not exist in any particular quarter.

Excluding 25 patients who had subtotal hysterectomies in the presence of undiagnosed cancer of the cervix, there were 393 patients with recurrent cervical cancer after previous radiation therapy or combinations of radiation therapy and surgery and who were treated by a variety of operations, chosen according to individual circumstances, with 99 (26 per cent) 5 year survivals.

DISCUSSION

There is a paucity of reports dealing with the problem of recurrent cancer of the cervix. Those published are concerned with very small groups culled out of very large series of patients and, therefore, as examples of what might be accomplished by one or another form of treatment have limited significance. For example, local destruction of recurrences sharply limited to the cervix or vaginal vault by means of actual or electro-cautery may be efficacious, but in how many instances among 300 to 500 patients can this be applied? Likewise, re-irradiation may be successful, but how often? It does not suffice to present excellent results in small numbers of selected

cases when in the majority of instances the methods cannot be applied.

The extent of the recurrences decides the manner of treatment and the results achievable. In Table III, Class A and B, there are 87 patients in whom recurrences presented in or adjacent to the cervix; 43 (50 per cent) were 5 year survivors after surgery. Once the recurrent cancer involves the parametrium (Class C), the prognosis falls appreciably (6 or 21 per cent, out of 29 cases). Such studies emphasize the desirability of obtaining surgical and pathologic classifications of the excised specimens, since a somewhat detailed extent of the recurrence can be related to the clinical result, an impossibility without a surgical specimen.

There seems to be only one major contribution in the literature dealing with recurrences after radiation therapy; the monograph published by Truelsen in 1949. This work includes a follow-up study of 390 cases treated by radium therapy which did not heal primarily; all were dead by the end of 2 years. Of 704 cases showing primary healing and then recurrences, 96.3 per cent of the patients did not survive over 5 years. The radiation techniques employed in the above series would not now be considered modern, the value of the study being what happened when recurrences occurred and were not treated.

If radiation therapy is to be employed in treating cervical cancer, a careful follow-up of the patients is obligatory even after prolonged intervals. If recurrences are detected and proven by biopsy (which might even necessitate laparotomy), appropriate surgical procedures are indicated without delay.

SUMMARY

The reported study is based upon 991 unselected patients with presumptive evidence of postradiation recurrences. In the series, 14 per cent did not actually have cancer. Of the remaining 853 with recurrence, 443 (44 per cent) were found to be operable. In 125 of these patients, less than pelvic exenterative operations were performed and 50 (40 per cent) lived 5 years. Of the 318 patients who underwent exenterations, 56 (17.6 per cent) survived at least 5 years free of disease.

The above series was comprised of a patient population cared for by outside physicians usually not cognizant of the potentialities of surgery for initial radiation treatment failure in cases of cancer of the cervix. Thus, better results might have been obtained had secondary surgical treatment not been delayed as long as it was in most instances.

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TREATMENT OF PRIMARY ADENOCARCINOMA OF THE CERVIX*

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THE treatment of primary adenocarcinoma of the uterine cervix is still somewhat controversial when the respective roles of radiation therapy and surgery are discussed. Since this variant of cervical cancer is relatively infrequent, divergent opinions concerning relative malignancy and methods of treatment have accumulated in the literature. This paper deals with the experience accumulated in the Department of Radiotherapy of the University of Maryland Hospital from 1956 to the end of 1964. This study was undertaken to better define the aspects of the tumor and to evaluate our current methods of therapy.

It is widely accepted that the treatment of choice of primary adenocarcinoma of the cervix is radiation therapy. While in the treatment of squamous cell carcinoma any postradiation surgery is thought to be unnecessary, in the therapy of adenocarcinoma of the cervix, the use of systematic surgery following radiation therapy has been widely advocated.

The reasons why several authors have been advocating the surgical procedure are the following:

(1) Adenocarcinoma of the cervix has been considered less sensitive to radiation than squamous cell carcinoma. This conviction is based on the general radiobiologic concept that all tumors of glandular origin, especially if secreting, are rather radioresistant. In this respect, the similarity of adenocarcinoma of the endometrium, notoriously more resistant to irradiation than squamous cell carcinoma, is also mentioned.

(2) As primary adenocarcinomas of the cervix are of endocervical origin, they are more likely to extend past the internal os than the squamous cell carcinomas in such cases the endometrial extension could be inadequately treated, becoming a source of future recurrence.

(3) In spite of all our diagnostic efforts including fractional curettage, P.A.S. staining, etc., a primary adenocarcinoma of the endometrium can be erroneously diagnosed as a primary lesion of the cervix. In a case where the uterine packing has not been carried out, the lesion of the endometrium will be inadequately treated.

In all such cases, total hysterectomy has been thought to be essential in order to remove any residual disease after irradiation which would be present at the level of the endocervix or endometrium. Hysterectomy has been carried out usually 6 to 8 weeks after radiation therapy and has been of different extent, ranging from simple hysterectomy to radical Wertheim procedures. The incidence of residual disease as reported from different authors has varied considerably, in some cases being as high as 53 per cent, as in the M. D. Anderson Hospital series. Such a high incidence of residual disease would seem at first glance to be an absolute indication for the surgical procedure. However, in analyzing the problem a little more closely, one would realize that the incidence of residual disease, rather than depending upon radioresistance of the tumor, can be due to other factors such as:

(1) Selection of cases—if surgery is done only in bulky tumors and if the early cases with good response to radiation are not operated upon.

(2) Modality of treatment—especially if in anticipation of the hysterectomy, the radiation dosage is reduced.

(3) Time interval between irradiation and surgery—the shorter the time, the greater the likelihood of residual disease. In

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TABLE I

RESULTS OBTAINED BY IRRADIATION AND COMBINED IRRADIATION AND SURGERY

Irradiation Alone			Irradiation Plus Surgery	
	5 Year Survival			5 Year Survival Adenocarcinoma
	Adeno-carcinoma	Squamous Cell Carcinoma		
Kottmeier[12]	44%	42%	Döderlein[6]	40%
Truelsen[21]	29%	28%	Bergsjo[3]	36%
Drescher[5]	24%	29%	Tremblay *et al.*[20]	35%
Marcus and Marcus[16]	40%	40%	Ward[22]	36%
Hepler *et al.*[11]	37%		Fletcher *et al.*[7]	47%
Sala *et al.*[18]	39%	36%		

University of Maryland: Adenocarcinoma = 60%; Squamous Cell Carcinoma = 62%.

fact, it has been suggested that adenocarcinoma of the endometrium or of the cervix could be a slowly regressing tumor and after radiotherapy sometimes requires several months to disappear completely.

(4) Finally, the fact that residual disease has been found in the specimen does not necessarily mean that the surgical procedure just carried out is a life saving procedure for the patient, since we do not know what the outcome of the disease would have been had the hysterectomy not been performed.

The opinions as to the advisability of hysterectomy after irradiation have been divided among different authors, and the results obtained by the advocates of hysterectomy are collected in Table 1 and are compared with the results obtained by irradiation alone.

There is no appreciable statistical difference between the results obtained with the two modalities of treatment. The 5 year survival in our series is no different from the one we obtain in squamous cell carcinomas. The analysis of such statistics seems to indicate that the surgical procedure is unnecessary in spite of the fact that a large percentage of specimens showed residual disease. In order to eliminate some of the possible causes of error in the evaluation of the results at the University of Maryland, we have established a policy in the treatment of adenocarcinoma of the cervix requiring:

(1) A full course of radiation therapy given radically with the same technique and dosage used in the treatment of squamous cell carcinoma of the cervix.

(2) Total abdominal hysterectomy to be carried out in all cases not less than 6 weeks after the completion of the treatment. Such a policy was established with the most complete agreement and collaboration of the Department of Gynecology and of numerous private gynecologists and ranged from simple total hysterectomy to radical Wertheim operation. One-third of the cases were not operated upon, either due to medical contraindications, the patient's refusal, or local extent of the disease.

Radiation therapy was given with the following modalities:

(1) Early cases—2 radium applications for 72 hours using the Fletcher system delivering a minimum of 7,000 rads to point A and supplementing the pelvic wall lymph node dose with parametrial technique with a minimum of 4,000 rads tumor dose in 4 weeks with telecobalt therapy.

(2) Bulky lesions and late cases—total pelvis irradiation up to 4,000 rads in 4 weeks to the midline, increasing the pelvic wall dose to a total of 5,000 to 5,500 rads

tumor dose, depending upon the extension, followed by one radium application for 72 hours.

Between 1956 and 1964, 42 cases of adenocarcinoma of the cervix were seen in the Department of Radiation Therapy of University Hospital, representing an incidence of 4.5 per cent when compared with the 938 cases of squamous cell carcinoma of the cervix treated during the same period of time. Of the 42 cases, 38 are included in the study, while 4 have been eliminated as they had been previously treated in other institutions either by irradiation or surgery. Of the 38 cases, 18 were classified as Stage I, 13 Stage II, 4 Stage III and 3 Stage IV.

Twenty-five cases or 66 per cent of the whole group underwent the complete treatment, that is, irradiation plus surgery. Thirteen cases had radiation therapy alone.

Analysis of all cases showing the incidence of residual disease, its effect upon survival and the results of irradiation alone are shown in Table II.

Forty per cent of the specimens showed residual disease. As was to be expected, positive specimens were more numerous in late cases than in early ones; approximately half of the cases with Stage II lesions which were operated on had residual disease as opposed to about one-third of Stage I cases. The fact that the specimens were positive does not seem, in our series, to adversely affect the survival. In fact, in both the positive and negative specimens, the survival is 80 per cent. If we now compare the results obtained by irradiation alone versus irradiation and surgery, it seems, at first glance, that the results obtained with irradiation alone were worse. However, we must point out that all patients in Stage IV were treated by irradiation only with palliative intent. If we eliminate Stage IV from this group, the survival is 80 per cent, which is exactly the same as in the irradiation plus surgery group. All deaths in the irradiation alone group were due to generalized and, except one, pelvic disease. The over-all results for all cases are shown in Table III.

These are 5-year results prepared with the Berkson-Gage Life Table Method and are statistically not different from our results of squamous cell carcinoma of the cervix where over-all survival is 62 per cent.

In the evaluation of a new modality of treatment, one should always ask oneself:

(1) Is there an improvement of results over the previous well established method?

(2) Is the new modality carrying with it a higher incidence of morbidity, rendering the new attempt not advisable?

In answer to the first question we can say that the expected improvement of the result has not been obtained.

The answer to the second question is found in Table IV.

Table II

INCIDENCE OF RESIDUAL DISEASE

	Irradiation Plus Surgery (25 cases)				Irradiation Alone (13 cases)	
	Positive Specimen		Negative Specimen		No. of Cases	Survival
	No. of Cases	Survival	No. of Cases	Survival		
Stage I	4	4 (100%)	10	9 (90%)	4	3 (75%)
Stage II	5	4 (80%)	5	3 (60%)	3	2 (66%)
Stage III	1	0 (0%)	—		3	3 (100%)
Stage IV	—		—		3	0 (0%)
Total	10 (40%)	8 (80%)	15 (60%)	12 (80%)	13	8 (61%)

TABLE III

FIVE YEAR SURVIVAL

	No. of Cases	Alive and Well
Stage I	18	86%
Stage II	13	56.5%
Stage III	4	60%
Stage IV	3	0%
Total	38	60% (standard error = 0.120)

Prepared with the Berkson-Gage Life Table Method.

TABLE IV

COMPLICATIONS

Irradiation Alone	Irradiation and Surgery
None	3 bowel adhesions with obstruction 3 fistulae (1 rectovaginal and vesicovaginal, 1 rectovaginal, 1 ureterovaginal) Incidence = 25% (1 complication mortal)

Any pelvic surgery following extensive irradiation carries with it an incidence of complications much higher than the one encountered after either of the two procedures done separately. While there were no major complications in the irradiation group, there was a 25 per cent incidence in the irradiation plus surgery group, most of them serious. Of course, this high rate of complication could only be accepted if the results of the combined therapy were better than the ones obtained with irradiation alone.

CONCLUSION

From the analysis of the results presented by other authors and from our own series, we can draw the following conclusions:

(1) There is no definite evidence that adenocarcinoma of the cervix is more resistant than squamous cell carcinoma.

(2) The high incidence of positive specimens, which was found in our series, in spite of the fact that radiation dosage was not changed and surgery was done at the proper time, can be explained on the basis of a different biologic response of the tumor which probably requires a longer period of time to disappear.

(3) The persistence of histologically detectable tumor in the cervix at the time of surgery does not seem to adversely affect the prognosis.

(4) Postirradiation hysterectomy does not modify the survival.

(5) The high incidence of complications following surgery performed in irradiated tissues contraindicates the procedure done in routine manner.

(6) Surgery should be considered only in those cases in which 2 months have elapsed since completion of therapy and which reveal clinical evidence of massive residual, still resectable disease, and, of course, in the postirradiation recurrences.

(7) The results obtained by radiation therapy in adenocarcinoma and in squamous cell carcinoma of the cervix are statistically similar.

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TRANSVAGINAL CESIUM 137 THERAPY*

By JEROME M. VAETH, M.D.,† HERMAN NUSSBAUM, M.D.,‡
and MARY LOUISE MEURK§
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THE indications and advantages of transvaginal roentgen therapy in the treatment of cancer of the cervix uteri have been stated by del Regato.[2,3,4] At the Claire Zellerbach Saroni Tumor Institute of San Francisco, the following indications for treatment of cancer of the cervix by transvaginal irradiation are recognized:

(1) Cancer of the cervical stump in which adequate intracavitary endocervical canal irradiation cannot be performed.

(2) Late stages of cancer of the cervix uteri in which whole pelvis irradiation to high doses has made intracavitary curie therapy to high doses hazardous to normal structures.

(3) Cancer of the cervix uteri in elderly patients or those considered poor anesthesia risks.

(4) Rapidly growing, exophytic, bleeding lesions of the cervix uteri in which situations intracavitary curie therapy is impractical, and external irradiation to high doses would be poorly tolerated. Adaptation of a cesium 137 teletherapy unit provides a practical method of applying transvaginal therapy.

Cesium 137 has an approximate half-life of 30 years and emits gamma radiation of 0.662 mev. energy, which compares favorably with a million volt x-ray machine. It possesses many of the advantages of supervoltage radiation therapy, *i.e.*, the absorbed dose per roentgen in muscle, fat, and bone is similar. Normal tissue is spared with a proper time-dose treatment schedule. A description of the source and the physical data are well presented by Botstein and Schulz.[1]

The authors, recognizing the theoretic



FIG. 1. del Regato transvaginal applicator, modified for use with Picker cesium 137 teletherapy unit.

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From the Claire Zellerbach Saroni Memorial Tumor Institute of San Francisco, Mount Zion Hospital and Medical Center.
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advantages of cesium 137 treatment, have been treating suitable cases of carcinoma of the cervix uteri and cervical stump with Cs^{137} radiation applied through a transvaginal applicator. The del Regato transvaginal applicator provides versatility, enabling the radiotherapist to properly irradiate the patient according to individual variations of vaginal tract anatomy. The del Regato applicator (3.5 cm. diameter) is modified by the addition of a brass plate to the cuff which collimates as well as provides coupling to the cesium 137 periscope collimator (Fig. 1 and 2). The treatment table is a cystoscopic table adjusted to place the patient in a modified Trendelenburg position (Fig. 3). The compactness and flexibility of the cesium 137 unit enable one to place the applicator within the patient's vaginal tract, approximate the machine to the applicator cuff and secure the applicator cuff to the cesium 137 therapy unit ring with ease. The relationship of the lesion with the applicator can be visualized through the periscope on the cesium 137 unit.

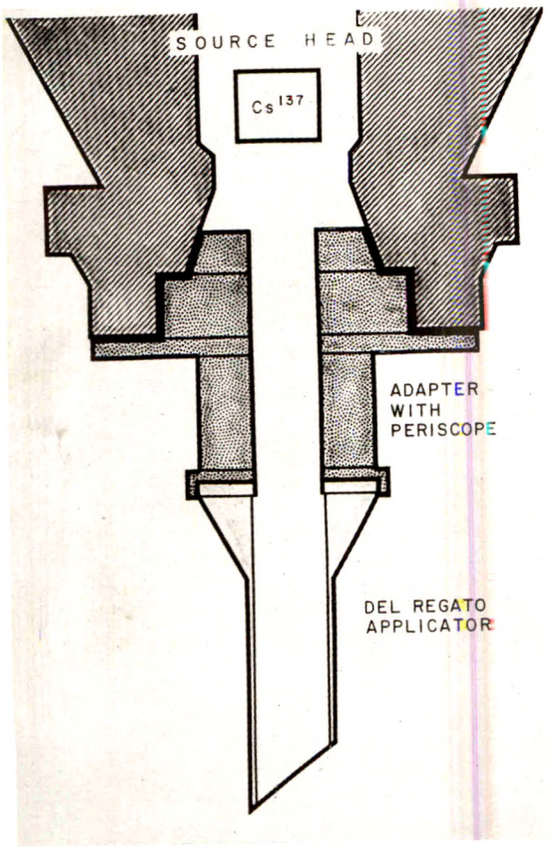


Fig. 2. Cut away view of del Regato applicator and cesium 137 unit joined together.

The isodose pattern of the transvaginal applicator is shown in Figure 4. It is somewhat similar to the isodose curves of the del Regato applicator with 0.5 cm. Cu half value layer radiations in doses delivered to the vaginal mucosa or outer surface of the applicator. An advantage of the cesium 137 dose distribution is the improved amount of radiation at a depth of 5 cm. with a rapid fall-off beyond.

A typical patient treated at the Saroni Tumor Institute was a frail, 80 year old woman, with a Stage IIB carcinoma of the cervical stump. Treatment to the whole pelvis was carried out with the cobalt 60 teletherapy unit, using opposing anterior and posterior pelvic fields without midline shielding. The dose delivered to the midplane in 50 days was 5,500 rads, treating 4 times weekly. Transvaginal cesium 137 therapy was then instituted, and 4,500 rads were delivered to the surface of the cervical stump in 9 treatments over 15 days. Treatment was tolerated well without bladder or bowel difficulties.

Further modification of additional vaginal applicators is presently being carried out. Adaptation of intraoral applicators is also contemplated because of the ideal quality of cesium 137 radiations and ease of maneuverability of the unit.

SUMMARY

1. Transvaginal irradiation is indicated in: patients with cancer of the cervical stump, with hemorrhaging cancer of the cervix, and in patients where intracavitary radium treatment is not possible for cancer of the cervix uteri.

2. Transvaginal cesium 137 therapy is made practical by adapting del Regato applicators to the teletherapy unit, and may be preferable to low kilovoltage radiations because of the better quality of its radiations and improved depth dose immediately beneath the mucosal and tumor surface.

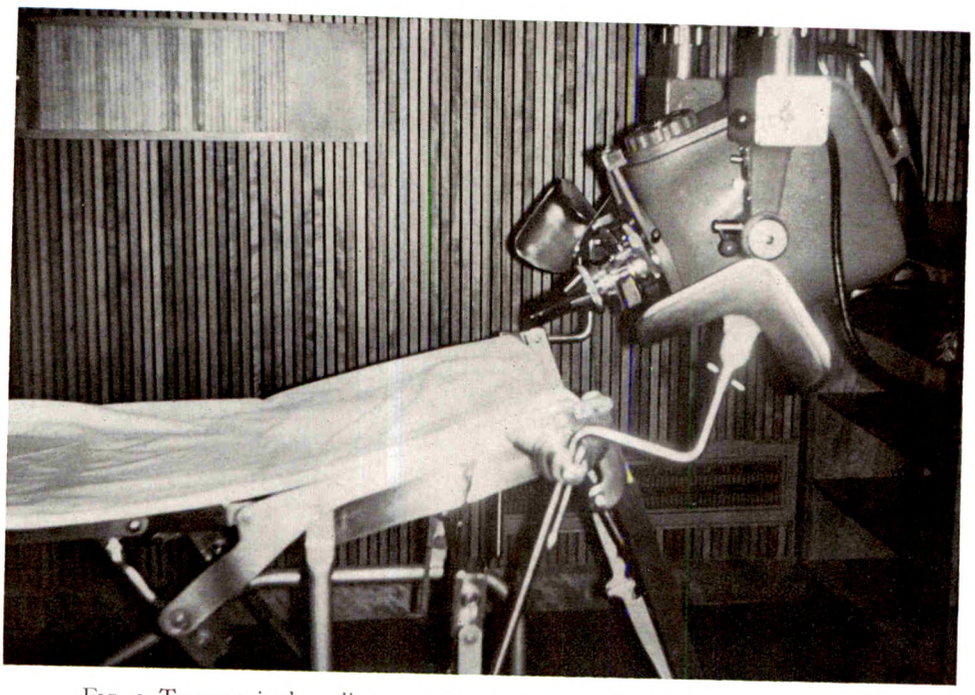


FIG. 3. Transvaginal applicator and cesium 137 unit with treatment table inclined to provide Trendelenburg position.

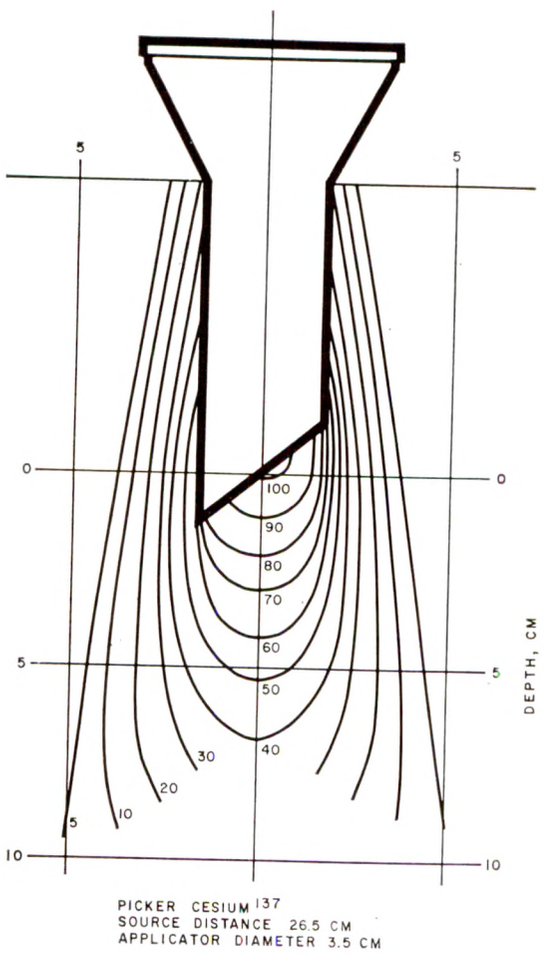


FIG. 4. Isodose pattern of cesium 137 with del Regato transvaginal cone. The dose at 5 cm. depth is approximately 53 per cent of that at the surface.

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Vol. 99, No. 2

OPAQUE PORTAL RULER FOR COBALT THERAPY*

WITH SPECIAL REFERENCE TO ITS USE WITH UTERINE CERVIX CARCINOMA

By MORTIMER R. CAMIEL, M.D., DAVID L. BENNINGHOFF, M.D., *and* LESLIE L. ALEXANDER, M.D.
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IT IS our practice to take preliminary "portal" radiographs through each prescribed cobalt therapy field to check the accuracy of its size, shape and position. This is done by placing an x-ray film in a cardboard holder under the patient or at the exit side of the body and making a small therapy exposure with the unit set up as if the patient were being treated through the prescribed portal. The resulting portal radiograph delineates the area actually being irradiated and permits shifting and adjusting of the field to more precisely desired limits.

The high penetrability of the cobalt ray results in radiographs of limited contrast. Bones particularly are poorly outlined and it is difficult at first to orient one's self to the usual landmarks. With some practice, however, one learns to interpret the cobalt radiograph with a confident degree of accuracy. Indeed, in some instances, as in the case of the respiratory system, the high air contrast furnished by the trachea and bronchi results in radiographs evocative of tomograms and are for some parameters superior to routine diagnostic roentgenograms.

However, the generally poor contrast has created the need for various opaque markers and rulers which can be more easily seen on the cobalt radiograph. We have devised a brass centimeter gauge of good opacity to the cobalt ray, which when placed in, on, or beside the patient during the portal film exposure, permits accurate delineation of some essential boundaries and insures their inclusion within the therapy field.

DEVICE

Following is a description of our device which can be copied easily by any tool or instrument maker with material at hand. Essentially, the device is a $\frac{3}{8}$ inch (1.0 cm.) in diameter brass rod, the shaft of which is tooled to half its diameter for every other centimeter, resulting in a centimeter ruler of good opacity to the cobalt ray. We chose this particular diameter for convenience to fit into the core of commercially available $\frac{5}{8}$ inch (1.6 cm.) in diameter lucite tubing which furnishes an esthetically acceptable and easily cleaned and sterilized surface (Fig. 1).

METHOD

A 23.0 cm. length of lucite tubing, $\frac{5}{8}$ inch (1.6 cm.) in diameter, with a $\frac{3}{8}$ inch (1.0 cm.) bore was sealed at one end by a lucite plug giving a 1.0 cm. lucite tip. The plug was cemented in place by chloroform. Because the instrument maker encountered some difficulty in tooling and fitting the entire length of brass tubing into the lucite bore, in this instance 2.0 cm. segments, alternating wide and narrow portions of 1.0 cm. each, were tooled separately and dropped sequentially into the tubing. The ruler was finished with a wide segment and its remaining end sealed with a 1.0 cm. plug similar to the first end. A 1.0 cm. brass ring was then permanently fixed around (instead of within) the first blank lucite end to opacify it and to mark the tip of the instrument. Another smaller brass friction ring was then fitted around the outside diameter of the lucite tube so that it could be moved to demarcate various land-

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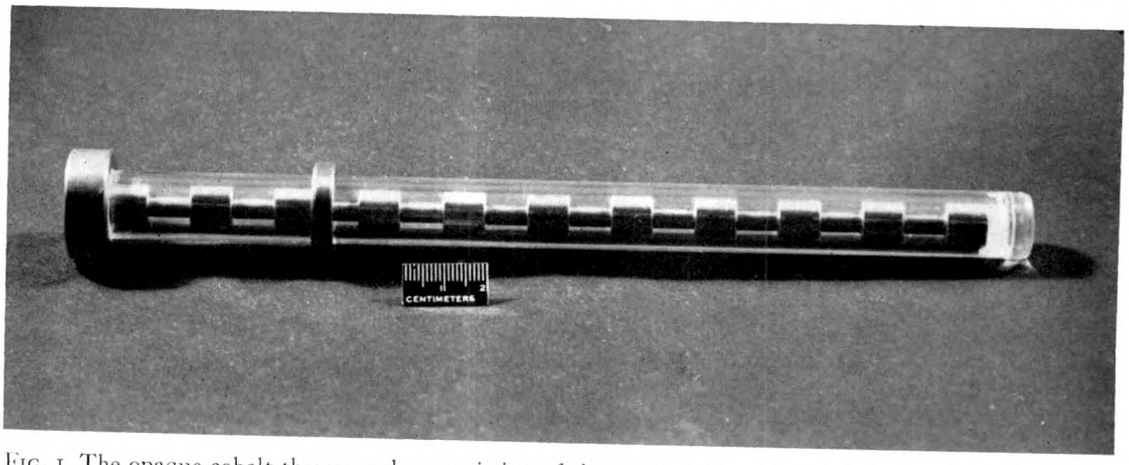


FIG. 1. The opaque cobalt therapy ruler, consisting of alternating wide and narrow 1.0 cm. lengths of brass within a transparent lucite tube. The instrument's tip is identified by a 1.0 cm. brass ring fitted permanently to one end. The smaller ring is of a friction type and may be moved along the tube to demarcate desired boundaries.

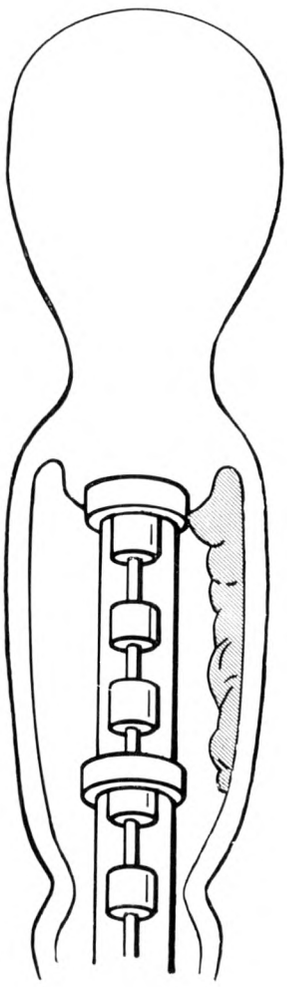


FIG. 2. Schema showing use of instrument with uterine cervix cancer. The tip of the instrument is placed against the cervix while the movable ring demarcates the lower edge of palpable disease.

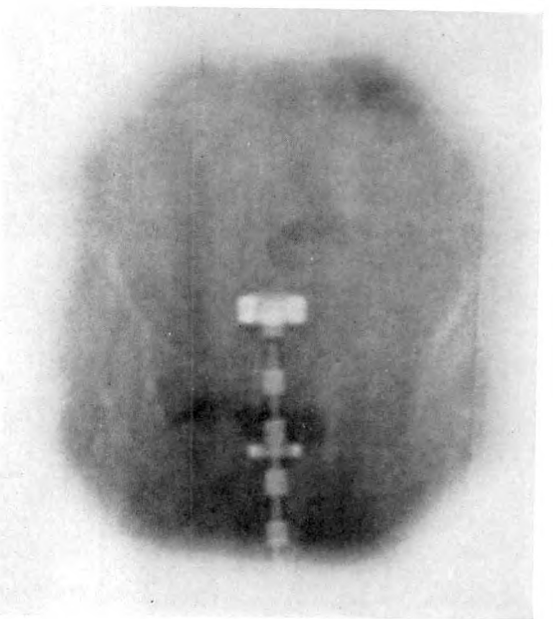


FIG. 3. Sample of cobalt portal radiograph for uterine cervix carcinoma showing the instrument in actual use. Its tip lies against the cervix. The smaller movable ring delineates the lowest palpable edge of the tumor and the portal extends downward from here for approximately 3.0 cm. plus allowance for penumbra. The bony pelvic outlines are barely visible.

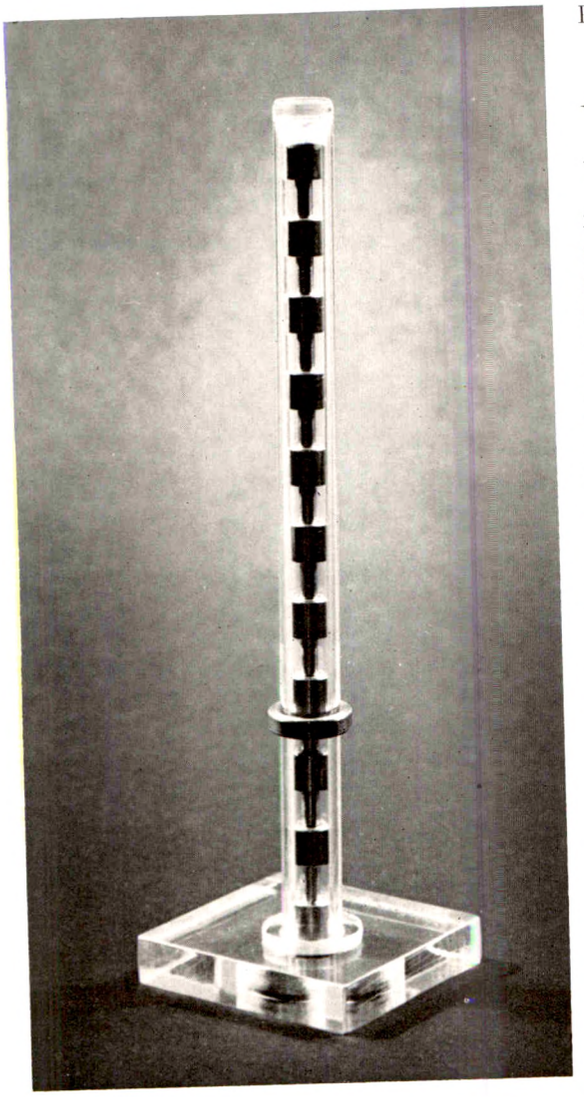


Fig. 4. The instrument may be used vertically by placing it in a lucite base.

marks (Fig. 1). The instrument could be immersed in zephiran chloride solution 1:750 for sterilization.

We have found the instrument particularly useful in localizing the fields for the rotational cobalt therapy of carcinoma of the uterine cervix. The cobalt treatment fields are localized in an anterior and lateral projection. The instrument is placed in the vagina so that its tip is against the cervix while the movable ring is placed at the level of the lowest palpable vaginal disease (Fig. 2). The lower edge of the port should be 3.0 cm. below the lower ring (Fig. 3). On the lateral view, the tip of the instrument is against the cervix and should be midway between the anterior and posterior edges of the portal.

Other uses for the device may be obtained by standing it vertically in a lucite base in which case it may be used to check laterally directed portals (Fig. 4).

SUMMARY

An opaque portal ruler for cobalt therapy is described and illustrated, with special reference to its use in cases of carcinoma of the uterine cervix.

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The radiologic instrument maker was Lawrence Rosario, A.A.S. The illustrations were furnished by the Medical Illustrations and Photography Department of Downstate Medical Center.

A DIRECT READING INTRACAVITARY DOSIMETER FOR USE IN RADIUM THERAPY*

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IN TREATING cancer of the vagina, cervix, or body of the uterus with intracavitary radium or external radiation, it is necessary to have a good estimate of the radiation dose absorbed by the bladder and rectum. Although the dose can be calculated from appropriate tables,[8,12,17,20] or from measurements made in phantoms,[1,11] it is desirable to obtain direct measurements in the patient. The development of miniature dosimeter systems permits such measurements to be made. These have consisted of two types: (1) an integrating or total dose indicator left in position either for a substantial portion, or for the entire treatment course, then removed and read out. These have been either small capacitor type ionization chambers, glass fluorods, or lithium fluoride capsules,[2,14,16] and (2) dose rate indicators, usually small ionization chambers, scintillation detectors, or semiconducting materials left in the body cavity for only short times.[15,19,21,23] Several critical reviews of both types of dosimeters suitable for intracavitary use have been published.[9,13,18,22] It is obvious from a review of the literature that every kind of dosimeter offers both advantages and disadvantages.

Some of the disadvantages encountered with most dose rate measuring instruments have been overcome by the lithium drifted silicon p-i-n junction dosimeters. The theory and application of such devices for dosimetry have been treated by Baily and his co-workers.[3–6] Specifically, these detectors offer the following advantages over conventional measuring instruments:

1. Small size. For example, a silicon detector is several orders of magnitude ($\sim 10^4$) more sensitive than an ionization chamber possessing the same active volume and requires less total volume in which to operate than either Geiger or scintillation counters.

2. Incorporation of such detectors in a small diameter ($\sim$3 mm. outside diameter) flexible sealed catheter is simple and inexpensive.

3. Good long term stability.

4. No voltage source, preamplifier, or phototube is required.

5. No electronics need be placed in close proximity to the detector. The electrical connections are brought out through the catheter to a simple and relatively inexpensive vacuum tube voltmeter ($\sim$50 feet of cable may be used between the detector and the voltmeter).

6. Immediate response. In contrast to other solid state dosimeters, such as cadmium sulfide, the high mobility of carriers in silicon produces an immediate meter response. Further, no predosing is required.

INSTRUMENTATION

The theory and operational characteristics of silicon particle detectors are comprehensively reviewed by Brown.[10] The utility of the p-i-n structure, with its relatively large volume for γ-ray detection and measurement, was pointed out by Baily *et al.*[7] and the response to gamma rays has been comprehensively studied.[4] In the application which we will discuss, the detectors are operated in a mode where the carrier generation due to gamma rays interacting with the bulk silicon is measured by means of the open circuit voltage induced by these carriers in the detectors

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
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Instrument development accomplished in cooperation with the Space Sciences Department of the Hughes Research Laboratories, Malibu, California.

used for this application. Approximately 50 per cent of the total detector volume is useful as a radiation detector.

A photograph of a typical catheter incorporating this type of detector is shown in Figure 1. The catheter is constructed using a light tight polyethylene tubing having an outside diameter of 3 mm. and a wall thickness of 0.010 inch. The end designed to be inserted in the body cavity is sealed with an epoxy cement which is inert to body fluids and is unaffected by ethylene oxide gas sterilization. The electrical connector is a standard Microdot unit. The electrical coaxial cable used is a low noise or antimicrophonic cable manufactured by the Microdot Corporation. The internal construction of three different dosimeters which were used in this study is shown roentgenographically in Figure 2. Such roentgenograms are taken of each catheter to localize the position of the sensitive volume for accurate calibration.

At low dose rates, such as in the application being discussed here, the response is essentially linear.[4] A typical calibration curve is shown in Figure 3. It can be seen that from about 1 r/hr. to a dose rate somewhat greater than 100 r/hr. the voltage generated is to a high degree of approximation a linear function of dose rate.

There are two difficulties which arise in the use of semiconductor detectors when they are operated in the mode being discussed. These have to do with temperature and wavelength dependence. First, with respect to wavelength dependence, it is

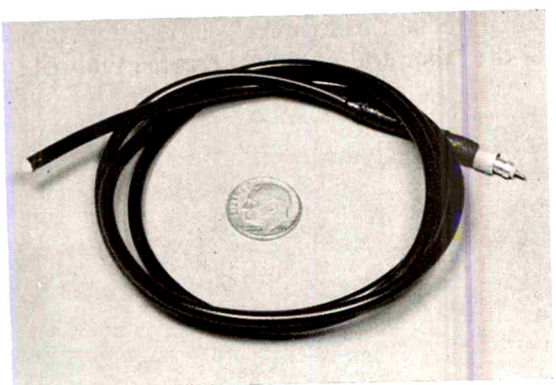


Fig. 1. Solid state intracavitary radiation probe.

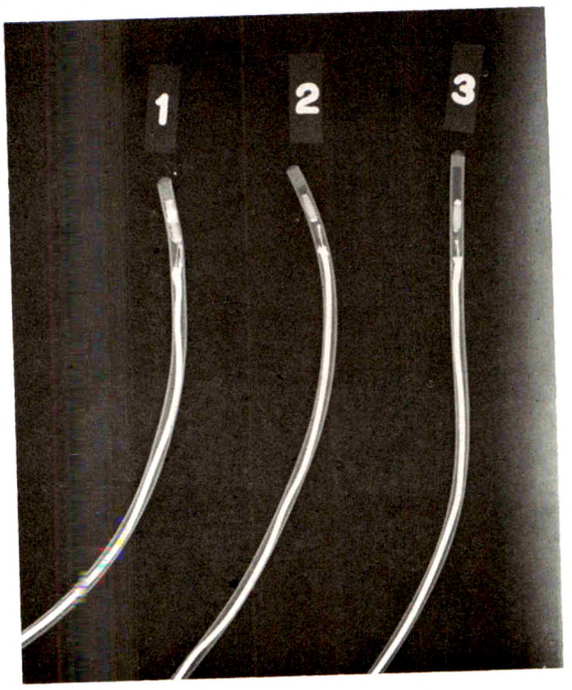


Fig. 2. Roentgenogram showing construction of intracavitary probe.

obvious that the number of carriers generated within the sensitive volume is a function of the absorption coefficient of the silicon. In small volume detectors such as used here, all carriers generated within the sensitive volume contribute to the voltage generated across the junction. The response should, therefore, be a function of the energy absorbed by this volume. For example, the ratio of the absorption coefficients of Co^{60} and radium are such that they should produce a response ratio of approximately 0.9, when the device is exposed to equal exposure rates. Experimentally,[4] a value of 0.83 was obtained. It is, therefore, recommended that an experimental determination of the calibration factor be made for each quality of radiation with which the dosimeter is to be used. Second, the temperature dependence is quite large, being approximately 5 per cent per degree centigrade in the range of the body temperature. Calibration procedures must also take this into account. Fortunately, the time constant for temperature equilibrium is short. A constant reading is reached in about 2 seconds following a

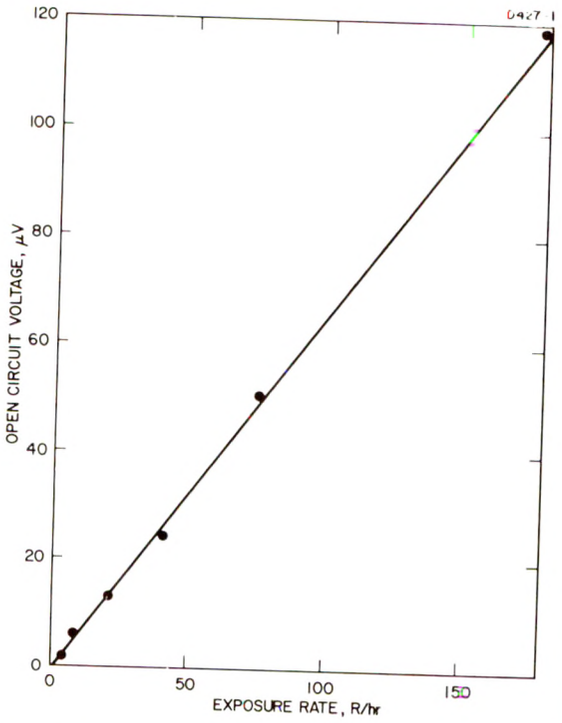


FIG. 3. Response of the intracavitary dosimeter to the gamma rays of radium.

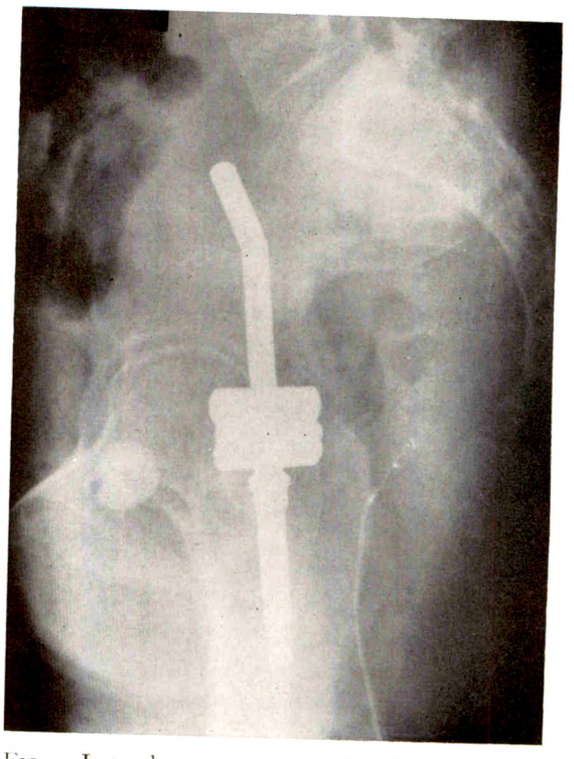


FIG. 4. Lateral roentgenogram of patient with both catheter and colpostat inserted.

change from room to body temperature.

CLINICAL EXPERIENCE

The readings obtained in the patient trials were in good agreement with those given in the Ansco publication authored by Ernst,[11] or with calculations made from linear radium dosage tables. In one comparison readings obtained with a Probitron were within 2 per cent of those obtained with the silicon detector. In a typical example, a crossed T configuration gave a measured maximum rectal dose rate of 30 r/hr. in good agreement with a calculated dose rate at the same point of 27 r/hr. In another example, a case utilizing Ernst technique number 2,[11] we measured a maximum dose rate of 21 r/hr. From the distances measured on diagnostic roentgenograms and the Ernst charts, a dose rate of 22 r/hr. was expected. However, it should be pointed out that the experimental value was the maximum that could be obtained, whereas the maximum shown for the rectum by the Ernst chart is 35 r/hr. It is certainly of value from a patient management point of view to know that no point in the rectum actually was receiving the higher dose rate. In the same patient, when she was retreated using Ernst technique number 20, a maximum of 18 r/hr. was recorded. The chart indicates a possible maximum of 33 r/hr., showing again the danger of using the charts to estimate maximum dose rates in the absence of precise anatomic knowledge.

Perhaps the greatest advantage in measuring dose rates directly is the avoidance of the labor and potential errors involved in measuring rectal-applicator distances from diagnostic roentgenograms. We have chosen 2 cases to illustrate this point. A lateral roentgenogram of the first case is shown in Figure 4. At first glance, this appears to be a normal roentgenogram, that is, the plane of the film is perpendicular to the central axis of the straight portion of the applicator residing in the uterine canal. The anteroposterior view showed the catheter to be slightly off center. If this were actually the

situation which existed, the Ernst chart would predict a value of the dose rate somewhere between 19 and 22 r/hr. for the point where the catheter resides. However, the measured value was 46 r/hr. If one examines this roentgenogram carefully and compares the length of the straight portion with that of the cross arms as measured from the roentgenogram and then compares this ratio with that of the actual dimensions of the applicator, it becomes obvious that the plane of the roentgenogram does not coincide with that of the central axis of the applicator. Correcting the measured distances for the angulation of the axis of the applicator with respect to the roentgenogram gives a corresponding chart value of 48 r/hr. The *in vivo* dosimeter showed that a range of dose rates from 20 r/hr. to 46 r/hr. existed in various portions of the rectum.

Another example of the difficulty encountered with roentgenograms is illustrated in Figure 5, *A* and *B*. In this case the maximum reading obtained in the rectum was 68 r/hr. The Ernst chart shows a maximum of 29 r/hr. in the rectum. Using the distances taken directly from the lateral roentgenogram and using the chart for this treatment plan (number 8), one would obtain a value of approximately 40 r/hr. Correcting for the distortion as evidenced by the shortened dimension of the straight portion of the applicator with respect to its actual length, the roentgenographic enlargement and the rotation shown by the anteroposterior view, which is obvious from the way in which the capsules on the arms are shown, the Ernst chart gives a dose rate of 74 r/hr., in agreement with the high experimental value obtained. As a result of the high dose rate measured, the applicator was repositioned.

CONCLUSIONS AND SUMMARY

We have reconfirmed the usefulness and

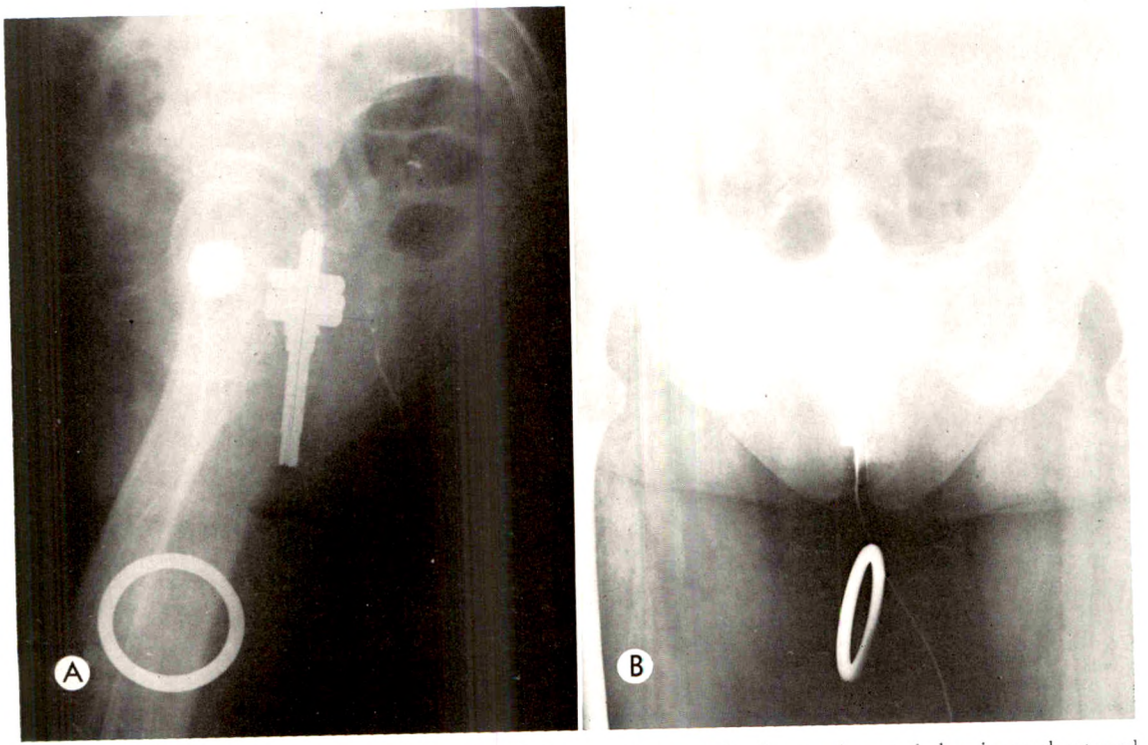


Fig. 5. (*A*) Lateral roentgenogram of patient with both catheter and colpostat inserted showing a shortened projection of the straight portion of the applicator within the uterine canal. (*B*) Anteroposterior roentgenogram of the same patient shown in *A*. This view is also distorted by a rotation of the film plane from that of the plane of the colpostat cross arms.

importance of making *in vivo* measurements of dose rate to various anatomic sites in patients undergoing radium therapy. The dosimeter described has specific advantages over other such instruments now in use. Chiefly among these are high sensitivity, rapid response, simple readout, and flexibility.

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TWENTY-FIVE YEARS' EXPERIENCE WITH SUPERVOLTAGE THERAPY IN THE TREATMENT OF TRANSITIONAL CELL CARCINOMA OF THE BLADDER*

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SINCE 1939, the senior author has consistently used supervolt radiation in the treatment of carcinoma of the bladder: first, in association with Dr. Simeon T. Cantril at the Swedish Hospital in Seattle, using 800 kv. and 2 mev., and since 1957, using 1 mev. and cobalt 60 at the University of California in San Francisco. The following report summarizes these long-term experiences.

SEATTLE EXPERIENCE

When Dr. Cantril and the senior author started at the Swedish Hospital in 1938, we had the advantage of well recorded cases of patients treated between 1934 and 1936 by our predecessors, Dr. Charles Ward and Dr. John Wirth. From the analysis of these cases, we learned to avoid some of the pitfalls which had not been appreciated during the early days of the use of supervolt radiation.

Of the initial group of 27 patients treated by Ward and Wirth between 1934 and 1936,[9,11,12] 5 were cystoscopically well for more than 4 years at the time of our first analysis in 1941.[2] These patients have remained alive for periods of between 6 and 23 years, as later follow-up observation indicated.[1,10] The technique of treatment of these patients differed somewhat from our own technique, to be described presently, insofar as the doses in some instances were significantly higher and the delivery time consistently more rapid. We believe, however, that the difference is not sufficiently great to exclude these cases from the analysis of curative results.

In 1941, Buschke and Cantril[2] reviewed for the first time the then accumulated material of 44 patients treated between 1934 and 1939. At that time, 7 patients were cystoscopically free of disease—5 for more than 5 years, 1 for more than 2 years, and 1 for 20 months. This series included many far advanced cases since there was no rational selection at that time.

The technique used in Seattle since 1939 did not appreciably change during the period under consideration here. We used one anterior suprapubic field and two oblique sacroiliac fields. The suprapubic field was often irradiated more heavily. We were not then as concerned with the introduction of a specific tumor dose as we are now. The treatment was carried to what was considered tolerable from the point of general condition and tolerance of pelvic structures, based on the then available experiences of our predecessors, on our own observations of intestinal tolerance during treatment, and on the extrapolation of our experiences with medium volt therapy of pelvic disease. Doses delivered to the bladder, as calculated in retrospect in some of the patients in this series, were rather low by present day standards—somewhere in the neighborhood of 4,500 r to 5,000 r in 35 to 45 days in most of the patients who have remained controlled.[5]

The purpose of the initial analysis[2] was an attempt to learn the reasons for the successes as well as for the failures and, if possible, to gain a more substantial working basis for the selection of patients in the future. By detailed analysis of every case,

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recorded in detail elsewhere,[2,5] we were indeed able to reach certain conclusions which, with minor modifications, were confirmed by our later analyses of larger material in 1942,[3] 1946,[4] 1950,[5] and 1957,[1] and which have been confirmed repeatedly by later experiences. Comparison of the successfully treated cases and the failures has permitted us to develop certain guiding principles which we have followed rather consistently since that time. *It became obvious that the result of radiological treatment differed critically, depending upon the microscopic grade of differentiation and on the presence or absence of invasion of muscle* (*stage*), an adage which is commonplace today.

The papillary carcinoma, Grade I, appeared entirely unresponsive to doses that can be safely introduced by external irradiation. Microscopic specimens of biopsies obtained before and after therapy look alike (see for instance Figures 99 and 100 in Reference 5).

Papillary carcinomas, Grade II and III, have been controlled in this group in a certain percentage of instances, *as long as they had not invaded the bladder muscle*, as determined by the recorded cystoscopic findings and analysis of the microscopic material.

We concluded at that time (1941): "All cases treated successfully represent papillary carcinomas without marked invasion of the bladder wall and in all probability without invasion of the muscular wall . . . In our group there is no case of an infiltrating carcinoma, either papillary or otherwise, which has been controlled by x-ray therapy." These conclusions were later somewhat modified when we had an opportunity to observe "cures" of far advanced infiltrating carcinomas, Grade IV, and some apparent cases of Grade III with apparently superficial muscular invasion (Stage B_1*).

* The staging used in this paper is the modification of Marshall's staging by the M. D. Anderson Hospital,[8] although the ambiguity of separating Stage B_1 from B_2 without examination of surgical specimen is fully appreciated.

In 1955, the senior author reviewed the material again and reported it in 1957.[1] This material cannot be evaluated according to stages, since we do not believe that an attempt at retrograde staging from the information available would be sufficiently reliable to make it useful. We can only state, therefore, that in this survey of patients treated at the Swedish Hospital in Seattle since 1934 (Table 1) *14 of 85 treated before 1950 had remained clinically and cystoscopically well for more than 5 years* (*16 per cent*). Of 66 patients treated between 1934 and 1945, 9 were well after 10 years (13 per cent). Three of these patients treated by us since 1939 were followed for 11 (A.L.), 19 (McG.), and 22 (E.A.A.) years, respectively, and showed normal bladder function at that time. Details of these cases have been recorded previously (Cases VII, VIII, and X in Reference 5).

It should be emphasized that these figures represent "cures" rather than survival. This means that these patients had normal cystoscopic findings and normal bladder function. This appears to be more meaningful for the evaluation of a treatment procedure, since many patients with transitional cell carcinoma of the bladder, in whom radiation therapy has been ineffective, may remain alive for many years in spite of uncontrolled disease. *We therefore consider treatment to be effective only if there is no recurrence that necessitates other forms of therapy after irradiation*, a standard applied in evaluation of most other cancers. There is, however, one reservation: we have observed (in the San Francisco series) 3 instances in which histologically apparently viable tumor was removed by transurethral resection 4 months, 5 months, and 7 months after irradiation without further recurrence for 5 years, 4 years, and 6 years, respectively.

SAN FRANCISCO EXPERIENCE

The technique used in the San Francisco material since 1957 has not differed appreciably from that previously used in Seattle. With 1 mev. and, since 1960, cobalt

Table I

CARCINOMA OF THE BLADDER TREATED BY RADIATION THERAPY AT THE SWEDISH HOSPITAL

Years	No. treated	Well, 5 yr.	Well, 10 yr.
1934–1950	85	14 (16%)	
1934–1945	66		9 (13%)

60 irradiation, the dose to the bladder was usually introduced equally through one suprapubic and two oblique sacroiliac fields. A few patients were treated with anterior arc rotation, and some of the large undifferentiated tumors were treated by parallel opposing pelvic fields for a homogeneous dose through the entire pelvis. Bladder doses were more accurately determined than in the earlier series, but treatment was still guided by close observation of intestinal and bladder symptoms, as well as constitutional tolerance. The doses ranged from 5,500 r in $5\frac{1}{2}$ weeks to 6,000 r in 7 weeks.

The junior author has recently reviewed the material from 1957 to 1962 and presented it at the meeting of the California Medical Association.[7] Of 100 patients seen (Table II), 59 were accepted for treatment. The great number of rejections (40 per cent) is at least partly explained by the excellent cooperation of our urological service. A senior staff member of our section attends every cystoscopy in this hospital where neoplasm is anticipated or suspected. Many of these patients are not candidates for radiation therapy, but for surgical management, observation by both radiation therapist and urologist, or for palliative care. Of the 59 accepted patients, 50 had transitional cell carcinoma and were treated by external irradiation (Table III). Fourteen were cystoscopically free of disease with good bladder function after 3 years (16 per cent), and 4 of 29 after 5 years (14 per cent). Considering only those without marked invasion of muscle (Stages A and B_1), the cure rate appears somewhat higher

Table II

CARCINOMA OF BLADDER CASES SEEN AT THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO 1957–1962

Patients seen	100
Patients accepted	59
Transitional cell carcinoma >Grade I	50

(25 per cent 3 year and 19 per cent 5 year cure rates), although the figures are too small for reliable conclusions.

COMPLICATIONS

During the early days when the disastrous effect of over-irradiation of the pelvic structures by supervoltage technique was not sufficiently realized, some severe late damages occurred. In 3 patients a severe pelvic fibrosis developed. In 1 of these, bladder capacity was reduced sufficiently to necessitate a transplantation of the ureter which was found to be dilated 4 times normal size. This patient died subsequent to transplantation. In another patient (L.P., Case IV in Reference 5) treated in 1935, a fibrosis of the bladder and rectum developed, with considerable discomfort through the years. The patient died 17 years later of complications from radiation damage

Table III

TRANSITIONAL CELL CARCINOMA OF BLADDER TREATED BY SUPERVOLTAGE IRRADIATION AT THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, 1957–1962

Stage*	No.	Alive		Controlled	
		3 yr.	5 yr.	3 yr.	5 yr.
Superficial A B_1	24	12/24 59%	7/16 44%	6/24 25%	3/16 19%
Deep B_2 C	13	2/13 15%	1/17 14%	2/13 15%	1/7 14%
D	13	0/13	0/6	0/13	0/6
Total	50	14/50 28%	8/29 28%	8/50 16%	4/29 14%

* We have used the modification of Marshall's classification by the M. D. Anderson Hospital.[8]

and the formation of a fistula between ureter and sigmoid in the absence of active disease. This patient had received approximately 10,000 r to the bladder in 63 days. A third patient (E.S., Case v in Reference 5) treated in 1936 with a bladder dose estimated by retrospective calculation to have been between 6,500 and 7,500 r in 47 days, had, after 10 years, progressing symptoms of pelvic fibrosis (rectal and bladder). In 1958 (22 years after therapy), bladder capacity was absent, an indwelling catheter was required, and a carcinoma "with epidermoid differentiation" (late recurrence or radiation carcinoma?) developed.

In none of the patients treated since 1939, either in Seattle or San Francisco, were there significant early or late complications. Rectal reactions of any degree were not observed and only occasionally did we observe a very transitory diarrhea. There was one exception of a patient who received in 1956 a dose of 7,500 r, in whom fibrosis of the bladder developed with the associated clinical symptoms.

We should also like to emphasize that in those patients who had survived for a sufficient length of time, we have never found on repeated cystoscopic examinations necrotic ulcerations in the bladder as we occasionally see after treatment of uterine carcinoma, in which this complication is undoubtedly due to the local radium application.

We are still unable to predict the degree of early radiation reaction to be expected in the individual case. We have seen very severe reactions in patients with adequate drainage and without excessive infection in whom, after the reaction has subsided, the lesion had remained controlled for periods of up to 15 or 20 years without any late damage and with normal capacity. On cystoscopic examination, the bladder mucosa was essentially normal (for instance, in Case VIII in Reference 5). In other instances the reaction is much less severe in spite of a similar dose and the treatment is supported easily. Obviously, we shall anticipate a more intense reaction with neoplastic involvement of the trigonal region, particularly in the presence of tumor extension into the urethral junction.

The number of patients in these 2 series is rather small. However, every patient in the Seattle series, throughout the entire course of treatment, was personally treated and followed by Dr. Cantril or the senior author, or both, and the observations in the San Francisco series confirmed our previous conclusions.

The repeated analyses of our observations during the last 25 years have prompted some modification of our earlier conclusions with regard to indications and limitations of external irradiation. We believe at this time the following conclusions to be valid:

1. Certain types of carcinoma of the bladder can be permanently cured by external irradiation with preservation of completely normal bladder function and without clinically significant tissue changes over observation times of more than 20 years.

2. There are 2 types of carcinoma of the bladder which are suitable for curative external irradiation:

a. The very undifferentiated carcinomas, Grade IV, which at times have been controlled even in the presence of very far advanced diseases (Stage C). These tumors usually present themselves as large bulky lesions. They have a short history because of their rapid growth and tend to invade diffusely through the bladder wall and into the lymphatics. For these reasons they are not suitable even for radical cystectomy.

b. Numerically, the most important group for external irradiation consists of papillary transitional cell carcinomas, Grade II and III, as long as the carcinoma has not or has only superficially invaded muscle. With regard to the indications for treatment of this group of carcinomas (Grade II and III), we have somewhat modified our conclusions, as previously mentioned. At the time of the initial analysis in 1941, it was concluded that we had not controlled these lesions in the presence of invasion of muscle, although at times they

have been arrested for several years. Since then, based on later experiences, we have come to believe that it is probably possible at times to control carcinomas that have invaded the muscle only superficially (Stage B_1). More advanced invasion of muscle (Stage B_2) may at times be controlled, but certainly not with consistency; in more advanced lesions we can probably not expect more than temporary arrest and retardation of progression, and even then at the risk of aggravation of symptoms. *Thus, it is extremely important that radiation therapy be instituted for this type of tumor prior to the massive invasion of muscle.* In previous years, we had suggested to the urologist that several attempts be made at transurethral procedures before a decision as to radiation therapy versus total cystectomy was reached, in the hope of making these lesions more radiovulnerable as they become more de-differentiated. We have changed this attitude during recent years because of the risk of more marked invasion of muscle, from delay in treatment. Prompted by our urologic staff, it is now our policy to treat this type of carcinoma (Grade II and III), if solitary, with one single initial thorough transurethral resection; to keep the patient under close observation with frequent cytological study and with cystoscopic examination every 3 months during the first year; and to proceed with external irradiation *at the time of the first recurrence* (either in the same place or elsewhere in the bladder). In the presence of multiple lesions, Grade II and III, at the time of initial consultation, we advise biopsy and immediate radiation therapy. Recurrence in the resected area itself is interpreted as incomplete removal; recurrence in areas distant from the original resected site or multiple lesions on first cystoscopy are assumed to indicate spread through the circumferential lymphatics of the bladder wall (although we are, of course, cognizant of the possibility of multifocal lesions). In either case, a more radical procedure which is effective over the entire bladder is indicated—either radical radiation therapy or cystectomy. Following irradiation, cystoscopy of the patient is again done every 3 months. If the disease is found uncontrolled 6 months after treatment, or has recurred after a free interval, radical cystectomy is considered.

3. With regard to technique for treatment of papillary carcinoma, Grade II and III, the senior author personally still prefers 3 stationary fields (suprapubic as the main field, complemented by oblique sacroiliac ports); some of his associates prefer arc rotation or parallel opposing fields. There does not seem to be a critical difference, because in the locally radiocurable Stages A and B_1 of Grade II and III carcinomas, pelvic lymph node involvement is unlikely. In very undifferentiated carcinomas (Grade IV), we now usually use parallel anterior and posterior ports to cover the entire pelvis homogeneously. We have, however, salvaged a number of these patients, also, by the use of the 3 field technique.

In the future, it is more important to attempt treatment of Grade II and III carcinoma earlier (before marked invasion of muscle) than to concentrate on efforts to improve treatment of advanced lesions. This necessitates a more universal understanding by the urologists of the place of irradiation in the treatment of cancer of the bladder. Experience in Seattle and San Francisco has shown that such an understanding develops following close cooperation with well trained radiotherapists.

SUMMARY

1. The senior author's personal experiences in the treatment of transitional cell carcinoma of the bladder with supervolt therapy since 1939 are reviewed with respect to curative results and late function of the bladder. The material includes the observations at the Tumor Institute of the Swedish Hospital, Seattle, and in the Section of Therapeutic Radiology of the University of California in San Francisco.

2. The technique consisted mainly of 3 stationary fields, using 800 kv., 1 mev., 2

mev., and cobalt 60 radiation. The doses delivered to the bladder in the Seattle series were around 4,500 to 5,000 r in 35 to 45 days, in the San Francisco material, 5,500 to 6,000 r in 5½ to 7 weeks.

3. Five-year "cures" by one course of radical radiation therapy were accomplished in the Seattle material in 14 of 85 patients (16 per cent), 10 year cures in 9 of 66 patients (13 per cent). In the San Francisco experience, the 5 year cure rate was 4 of 29, or 14 per cent. "Cure" means cystoscopically and functionally normal bladder without recurrence at any time.

4. In all of those patients treated since 1939 who remained cured over periods of up to 22 years, the bladder function was entirely normal. Fibrosis in this material was observed in only 1 patient who received 7,500 r bladder dose. In the material treated before 1939, following excessive doses during the early years of the use of supervolt therapy, some severe late pelvic damage was observed. From this material and from reports in the literature[6] it appears that a 6,000 to, at most, 6,500 r bladder dose (with fractionation of 900 to, at most, 1,000 r per week) is the limit of consistent tolerance of the bladder.

5. Suitable for radical external irradiation are 2 types of transitional cell carcinoma: very undifferentiated carcinomas (Grade IV) regardless of the pelvic extent, and carcinomas, Grades II and III, prior to invasion, or at least prior to massive invasion, of the muscle. The author's present policy in the treatment of solitary lesions of Grade II and III consists, therefore, in recourse to radical radiation therapy after the first recurrence following thorough transurethral resection. In the presence of multiple lesions at first cystoscopy, primary radiation therapy is recommended. In Grade IV carcinoma, radiation therapy is the immediate method of choice.

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VOL. 99, NO. 2

THERAPY OF LYMPHANGIOSARCOMA OF THE CHRONICALLY EDEMATOUS LIMB*

FIVE YEAR CURE OF A PATIENT TREATED BY INTRA-ARTERIAL RADIOACTIVE YTTRIUM

By JULIAN B. HERRMANN, M.D., F.A.C.S., *and* IRVING M. ARIEL, M.D., F.A.C.S.
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LYMPHANGIOSARCOMA; a highly malignant neoplasm of the edematous extremity, was first described in the upper extremity by Stewart and Treves[30] in 1948. It occurs most frequently in the postmastectomy edematous limb, although it has been found, on a few occasions, in chronic edema of the upper extremity unassociated with mastectomy.[10,24,28,31]

Postmastectomy lymphangiosarcoma is relatively uncommon. Only 83 authenticated cases have been reported to our knowledge in the 17 years since its description; undoubtedly, there have been unreported instances.[13,14] On occasion, it may have been considered metastatic breast cancer, especially the hemorrhagic type,[12] or Kaposi's sarcoma, either of which it may resemble macroscopically or even microscopically.

Lymphangiosarcoma of the chronically edematous lower extremity is even more uncommon. Only 12 authenticated cases have been reported.[1,2,8,10,17,18,19,20,21,31,32,33]

An extensive review of the literature on lymphangiosarcoma of the edematous extremity has recently been completed by one of us (J.B.H.).[14] The prognosis was grave regardless of the treatment used. In general, there were three types of therapy: biopsy and subsequent external irradiation; wide excision of the neoplasm with or without skin grafting and with or without associated irradiation; and, extensive surgical procedures such as simple amputation, disarticulation, forequarter amputation and hemipelvectomy. In a few instances, chemotherapeutic agents were used, sometimes in conjunction with external irradiation.[5,15,16,22] We know of no instance where the intra-arterial administration of radioactive isotopes in the treatment of this sarcoma has been used.

We report the results obtained from the use of intra-arterial radioactive yttrium (Y^{90}) microspheres* in a patient with postmastectomy lymphangiosarcoma and evaluate the various therapeutic procedures that have been used for this sarcoma.

REPORT OF A CASE

B.P., in 1940, at the age of 42 years underwent a right radical mastectomy for an infiltrating ductal carcinoma, Grade III, with metastases to the ipsilateral axillary lymph nodes at level one. Post mastectomy, she received 1,500 r (120 kv.) to the right anterior chest wall, 2,000 r (250 kv.) to both an anterior and posterior right axillary port, and 1,200 r (250 kv.) to a direct axillary port. Intense edema of the right arm, forearm and, to lesser extent, of the dorsum of the hand appeared shortly after the operation and persisted unchanged for the subsequent 20 years. As a result, no motion was possible at the shoulder, elbow or wrist, although there was function of the right hand. Her health had been good except for attacks of cellulitis in the edematous extremity and concomitant hyperpyrexia.

In 1960, at the age of 62 years, the patient found a mass in the left breast. This was clinically a carcinoma. The right arm measured 42.5 cm. and the left 27.5 cm., midway between the acromiom and olecranon processes. There was no roentgenologic evidence of metastasis either to the skeleton or lungs. The serum calcium, phosphorus and alkaline phosphatase determinations were within normal limits and no malignant cells were present in a sternal marrow aspirate. A left radical mastectomy was performed (J.B.H.) on January 10, 1961. The

* Supplied by 3M Co., St. Paul, Minnesota.

* From the Department of Surgery, New York Medical College and Metropolitan Medical Center, New York, New York.

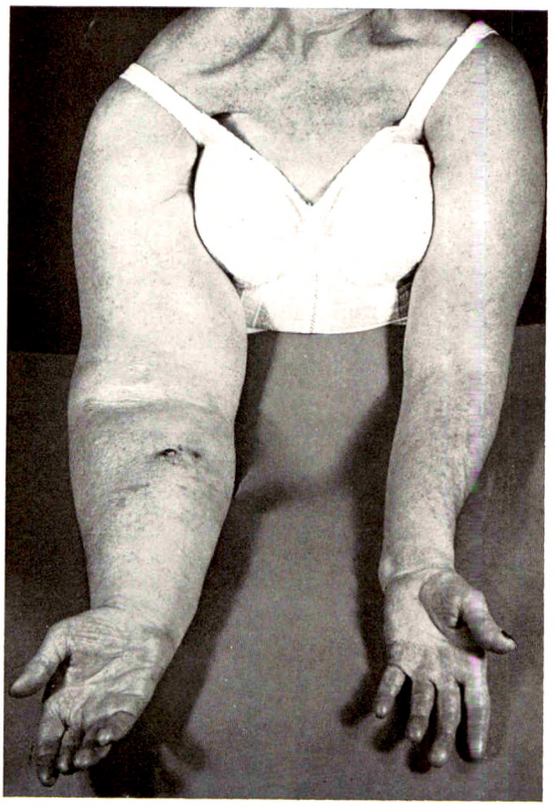


FIG. 1. Clinical photograph, taken shortly after the appearance of the sarcoma, shows the markedly edematous right arm and forearm and the small localized group of dark purplish nodules of lymphangiosarcoma just below the antecubital fossa. There is minimal edema of the right hand.

pathologic report was that of an infiltrating duct cell carcinoma; no metastases to the axillary lymph nodes were present. The incision healed per primam. No postoperative irradiation was given.

The patient was examined at monthly intervals and, with the exception of one attack of cellulitis of the edematous right upper extremity, was asymptomatic with no evidence of recurrent or metastatic carcinoma. Examination in early May, 1961, revealed no evidence of edema of the left upper extremity and no increase in the edema of the right upper extremity. About 3 weeks later, she noticed the sudden appearance of some black and blue marks on her right forearm (the edematous extremity). Examination disclosed a 2 by 3 cm. zone of confluent bluish-black nodules on the volar surface of the right forearm below the antecubital space (Fig. 1). This appeared to be lymphangiosarcoma; the diagnosis was confirmed by histologic examination (Fig. 2).

In July, 1961, radiation therapy (220 kv., ½ mm. Cu and 1 mm. Al filtration) was administered through a volar port measuring 18 by 7 cm., extending from above the antecubital fossa to the wrist; 150 r daily for a total skin dose of 3,060 r. Therapy was continued with 11 treatments of cobalt 60 through the same port, for a total skin dose of 2,764 r and 2,100 r at a depth of 4 cm. The combined dose from the two modalities was 5,824 r at the skin and 4,400 r at a depth of 4 cm. given over a period of 5 weeks with a fairly severe moist reaction and skin denudation.* There was transient regression of the nodules but fresh ones began to appear in the irradiated field and elsewhere on the extremity within a month after termination

* The external irradiation was administered by Dr. Henry Goldberg.

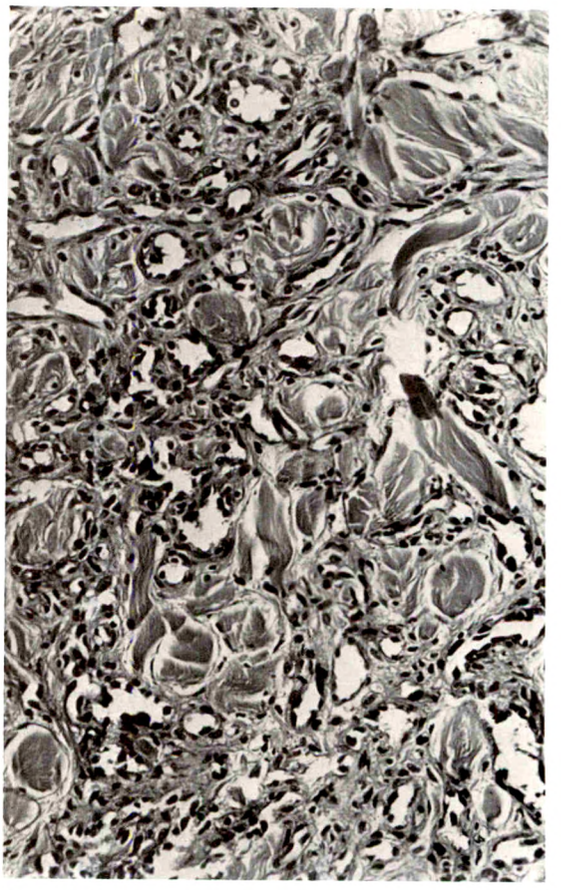


FIG. 2. Photomicrograph of the biopsy specimen showing the sarcomatous vascular channels lined by plump endothelial cells (lymphangiosarcoma).

of the radiation therapy. They increased in number and size, extended down the forearm to the wrist, up the arm to the axilla, and onto the dorsum of the upper arm and the skin over the scapula (Fig. 3). There was no increase in the circumference of the right arm or of the forearm and there was no edema of the left upper extremity. Amputation of the sarcomatous extremity was advised several times, but refused.

The sarcomatous nodules continued to increase in size and number. In February, 1962, under local anesthesia, 40 mc of radioactive yttrium (Y^{90}), incorporated in ceramic microspheres, was injected by direct puncture through the skin into the right subclavian artery (Fig. 4). The microspheres are carried to the small arterioles and capillaries where they lodge and irradiate the adjacent structures. The exposure of the tissues to intense irradiation is relatively short, inasmuch as the half-life of the isotope, Y^{90}, is $2\frac{1}{2}$ days.[3,9,23]

The "3M" brand irradiating microspheres are ceramic, completely inert chemically and physiologically and have an absolute density of 3.0 gm./cm.^{3}. They can be manufactured to measure from 1 to 200 microns in diameter; the spheres used for this patient measured 50 ± 10 microns. Yttrium 90 is bound to the microspheres; it is a pure beta emitter with an aver-

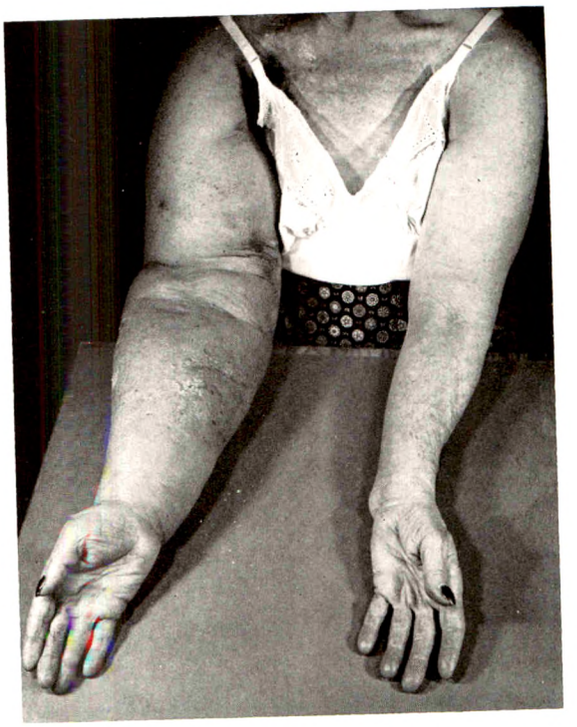


Fig. 3. Clinical photograph taken 4 months after external irradiation of the forearm. The scar of the excision of the lesion can be seen. Tiny bluish and pinkish nodules have appeared in the irradiated regions of the forearm and nodules of sarcoma are now present in the upper arm.



Fig. 4. Clinical photograph, taken about 1 month after the injection of yttrium 90, shows the wide distribution of the sarcomatous nodules. They now extend from the wrist to the mid-part of the upper arm. They were also present on the back of the forearm, upper arm and the skin over the scapula. Moderate edema of the right hand and fingers is now present.



FIG. 5. Clinical photograph, taken 2 months after the yttrium 90 injection, shows flattening and beginning regression of the sarcomatous nodules. Some faint brownish pigmentation of the skin can be seen at the sites formerly involved by some of these nodules. Marked edema of the right hand and fingers is now present.

age β energy of 0.93 mev. It is difficult to determine the dose administered to the neoplasm, although it has been calculated that 0.6 mc Y^{90} will deliver 1,000 rads beta radiation to a 100 gm. spherical organ. Therefore, the dose delivered by the 40 mc Y^{90} would depend upon the distribution of the isotope and the weight of the tissue being irradiated. These data are not available.

Subsequent to the injection of the yttrium, there was great pain in the extremity, necessitating the use of demerol (meperidine) and there was increased edema of the right hand and fingers. Within 3 weeks the skin nodules began to flatten and change from a bluish-black to a brownish color (Fig. 5). This continued and the sarcomatous nodules gradually regressed, faded, and disappeared until at present, 5 years after the onset of the lymphangiosarcoma, there is no external evidence of sarcomatous neoplasia (Fig. 6), and roentgenologic studies have revealed no evidence of metastasis to either the lungs or bones. One of the patches of fading skin pigmentation was biopsied and reported as thickened dermis incorporating scattered small pigmented granules with no evidence of atypical or malignant cells (Fig. 7).*

The intense neuritic pain in the extremity persisted for several months and the edema of the fingers and hand has remained unchanged, resulting in greatly diminished hand function. Circulatory blockage by the microspheres may be a contributory factor in producing the edema. Peripheral pain occurring in the hands or feet and persisting from 2 weeks to 2 months has been associated with the injection of the microspheres into an artery supplying an extremity, whereas edema has not been observed in 8 patients so treated for various neoplasms.

* Pathologic studies made by Dr. Charles Karpas.



FIG. 6. Most recent photograph taken December, 1965. There is no evidence of the sarcoma and the brownish pigmentation has been completely absorbed. The edema of the right hand and fingers has persisted unchanged.

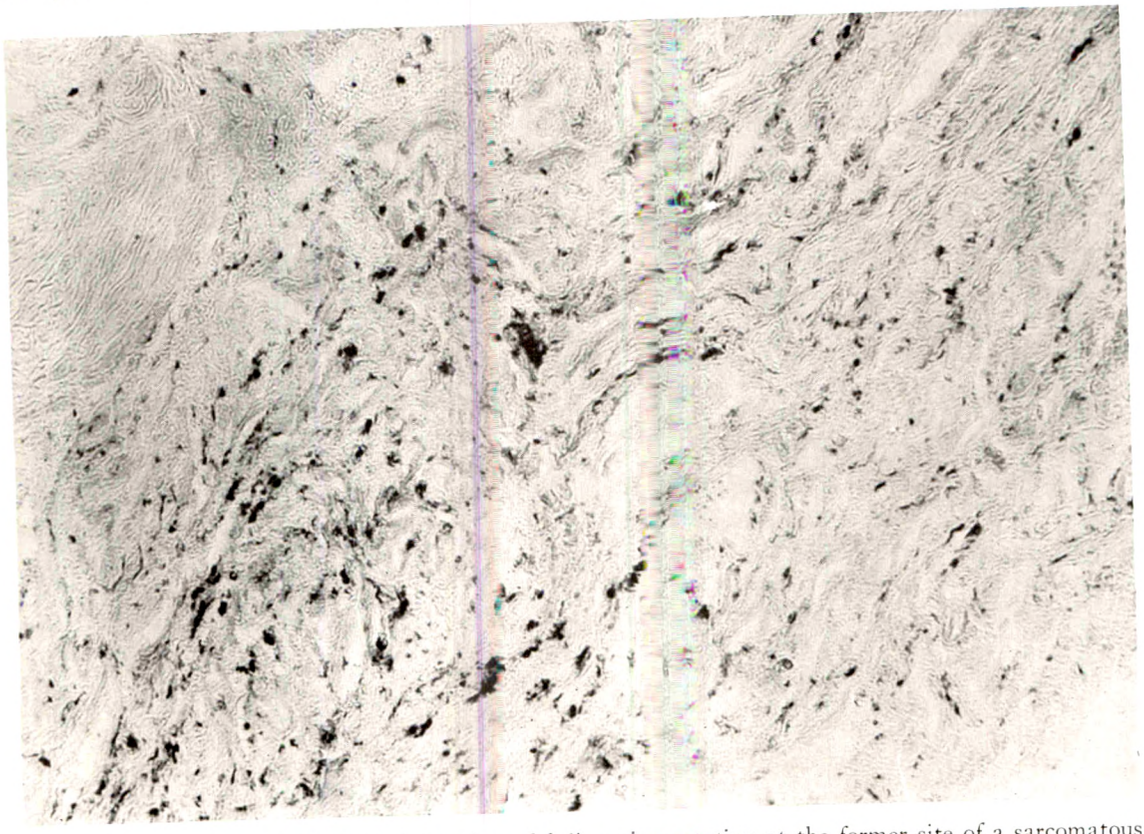


Fig. 7. Photomicrograph of a biopsied region of fading pigmentation at the former site of a sarcomatous nodule. Dark-staining pigment granules enmeshed in a fibrous stroma are scattered throughout. No malignant cells are present.

DISCUSSION

The results of treatment of lymphangiosarcoma of the chronically edematous limb have been disappointing. Of the 75 postmastectomy lymphangiosarcomatous patients, with an adequate period of observation subsequent to the initiation of attempted curative treatment for the lymphangiosarcoma, only 5 have survived 5 or more years, apparently free of sarcoma; 1 patient was treated solely by external irradiation,[29] 1 by wide excision of the sarcoma,[7] and 3 patients by extensive surgical procedures.[4,6,31] With the exception of these 5 patients, the mean survival period was 18.6 months after onset of the sarcoma. Supplementing external irradiation with chemotherapy has not appeared to influence the results.

The patient herein reported had a transient favorable response to external irradiation but a persisting favorable response to internal irradiation and is apparently free of sarcoma 5 years after its onset. With the exception of Southwick and Slaughter's[29] patient, who is living 13 years subsequent to external irradiation,* only 3 other patients have been reported who had a relatively long but less than 5 year survival subsequent to external radiation therapy of postmastectomy lymphangiosarcoma. These 3 women died of their sarcoma 40 months,[27] 41 months,[26] and 48 months[25] subsequent to the initial manifestation of the sarcoma. With the exception of our patient and that of Southwick and Slaughter, the mean survival of the 25 patients treated solely by irradiation was 18.5 months. The treatment of lymphangiosarcoma of the chronically edematous upper

* Personal communication.

extremity unassociated with mammary carcinoma also has been unfavorable.

The results of treatment of lower extremity lymphangiosarcoma likewise have been unsatisfactory; only 2 of the 12 reported patients had a lengthy survival. Both had a thigh amputation; 1 patient has survived 6½ years[31] and the other who lived 22 years may have had Kaposi's sarcoma.[11]

One patient, unreported, with Kaposi's idiopathic hemorrhagic sarcoma of the leg, treated by the administration of intra-arterial Y^{90} microspheres, manifested a marked regression of sarcomatous nodules. He died of a coronary occlusion 24 months after treatment.

Inasmuch as lymphangiosarcoma is radiosensitive in some instances, it may be advisable initially to use combined external and internal irradiation. If there is little or no response to irradiation, or if there is widespread recurrence in the extremity after an apparently satisfactory regression, then surgery must be considered.

SUMMARY AND CONCLUSIONS

The results of treatment of lymphangiosarcoma of the chronically edematous upper and lower extremity have been reviewed. For the most part, the response has been unfavorable regardless of the therapy utilized.

Of 75 reported postmastectomy patients with upper extremity lymphangiosarcoma treated in an attempt to cure this sarcoma, only 1 patient treated solely by irradiation, 1 by wide excision only, and 3 patients treated by extensive surgical procedures have survived apparently free of sarcoma for 5 or more years. The mean survival period of the treated patients who died of the sarcoma was 18.6 months.

Of the 12 reported patients with lower extremity lymphangiosarcoma, only 2 have survived the onset of the sarcoma for 5 or more years. Both were treated by amputation of the extremity.

A patient is reported with postmastectomy lymphangiosarcoma who was treated initially by external irradiation with transient benefit and subsequently by the intra-arterial injection of radioactive yttrium (Y^{90}) microspheres. She is apparently free of the sarcoma at present, 5 years after its onset. With the exception of the 1 living 13 years after appearance of the sarcoma, our patient to date, has the longest survival free of evidence of sarcoma of the reported patients treated solely by irradiation.

The undesirable sequelae of treatment in the patient herein reported were the intense, long-lasting pain in the limb, persistent edema of the fingers and hand and impaired hand function.

External irradiation in combination with the intra-arterial administration of radioactive substances may prove effective in those patients whose sarcoma is radiosensitive. It may be desirable to try this technique initially; if unsuccessful, radical surgical resection of the extremity is the indicated procedure.

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EMBRYONAL RHABDOMYOSARCOMA*

FIVE YEAR SURVIVAL OF A PATIENT TREATED BY RADIATION AND CHEMOTHERAPY

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WITHIN the past 5 years there have been several excellent articles dealing with the clinicopathologic aspects of the entity known as "embryonal rhabdomyosarcoma." The subject has been presented from various aspects by pathologists,[1,13] surgeons,[10] radiotherapists,[4,6,9,14] and chemotherapists.[7,11] Recently, this author[4] discussed the treatment of 20 cases of embryonal rhabdomyosarcoma from the standpoint of radiotherapeutic responsiveness and local radiocurability. Ten of our cases had primary lesions in the head and neck region. One of our patients now has survived 5 years from the time of treatment, and, considering the natural history of embryonal rhabdomyosarcoma, apparently has been "cured."

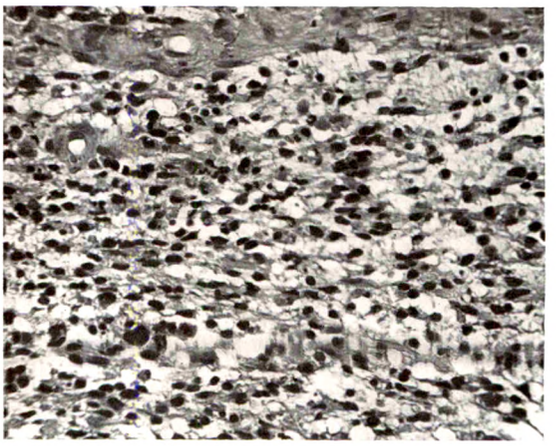


FIG. 1. Botryoid embryonal rhabdomyosarcoma. Low-power view. Note the embryonal and mesenchymal nature of this infiltrating supporting tissue neoplasm.

REPORT OF A CASE

At the time of original presentation, the patient was an 11 year old white male, who developed symptoms of bilateral nasal obstruction in September, 1960. An apparently uneventful tonsillectomy and adenoidectomy was performed in November, 1960. Pathologic examination of the tissues removed was not done at that time. The symptoms of nasal obstruction returned and on May 8, 1961, a biopsy of the recurrent nasopharyngeal mass was performed at Kent General Hospital, Dover, Delaware. Considering the gross polypoid appearance of the material removed, as well as the histologic pattern, a diagnosis of embryonal rhabdomyosarcoma, botryoid variant (Fig. 1 and 2), was returned by the Pathology Service, Walter Reed General Hospital. The pathologic material was reviewed by Dito and Batsakis.[2,3] The patient was referred to the Radiotherapy Clinic, Walter Reed General Hospital, where the physical examination prior to the institution of radiotherapy was otherwise essentially negative, and no abnormal masses or lymph nodes were palpable in the neck. A chest roentgenogram was normal.

Over a period of 39 days from May 16 through June 23, 1961, the patient received a telecobalt rotational nasopharyngeal tumor dose of 6,750 rads through a 5×6 cm. field in 27 increments. No significant skin reaction could be detected at the completion of the course of radiation therapy. The patient received intravenous actinomycin D during the first 12 days of radiation treatments, to a total cumulative dose of 75 μg./kg., or a total of 3.0 mg. The patient did exceedingly well. The tumor regressed and moderate mucositis and edema subsided rapidly, so that by September 1961 on examination the nasopharynx had returned to a normal appearance.

On a routine follow-up chest roentgenogram

* From the Radiology Service, Tripler General Hospital, Honolulu, Hawaii. This material has been reviewed by the Office of the Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any endorsement of the opinion advanced or any recommendation of such products as may be named.

† Chief, Radiation Therapy Section, Tripler General Hospital, Honolulu, Hawaii. Formerly, Research Fellow and Assistant Chief, Radiation Therapy Section, Walter Reed General Hospital, Washington, D.C.

on November 14, 1961, however, a parenchymal mass density above the right hemidiaphragm was noted (Fig. 3). Further delayed roentgenograms confirmed a rapidly enlarging mass in the right lower lung field and accordingly a metastatic nodule was diagnosed clinically. Over a 29 day period from December 5, 1961 to January 3, 1962, 5,500 rads tumor dose was delivered through 5×5 cm. parallel opposing coplanar portals in 20 increments, employing a 2 mev. resonance transformer unit (half value layer 8.0 mm. Pb).

During the first 2 weeks of this second course of radiation therapy, the patient received actinomycin D daily, intravenously, at a dose of 4 μg/kg. The patient had mild nausea and vomiting with the institution of the actinomycin D therapy; however, this subsided rapidly after the first 2 weeks of therapy. The white blood cell count and platelets remained within normal limits and the patient was discharged from the hospital to home care, to be followed at regular intervals.

Since that time the patient has been followed at regular intervals (Fig. 4), both at the Walter Reed General Hospital, and, more recently, at the Head and Neck Clinic of the Temple University Hospital in Philadelphia. There is no evidence of disease in the nasopharynx and a recent chest roentgenogram is also negative. The patient is in good health and 5 years have passed since his original treatment for botryoid embryonal rhabdomyosarcoma of the nasopharynx.

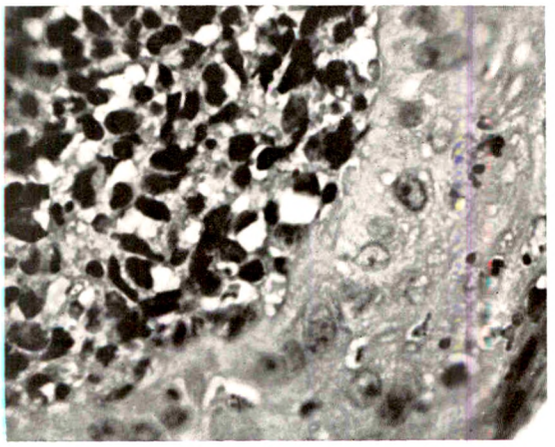


FIG. 2. Botryoid embryonal rhabdomyosarcoma. Note the "cambium layer of Nicholson." This is a multilayered band of short spindle cells with relatively little cytoplasm lying parallel to the mucosal surface of the tumor just beneath the mucosa.

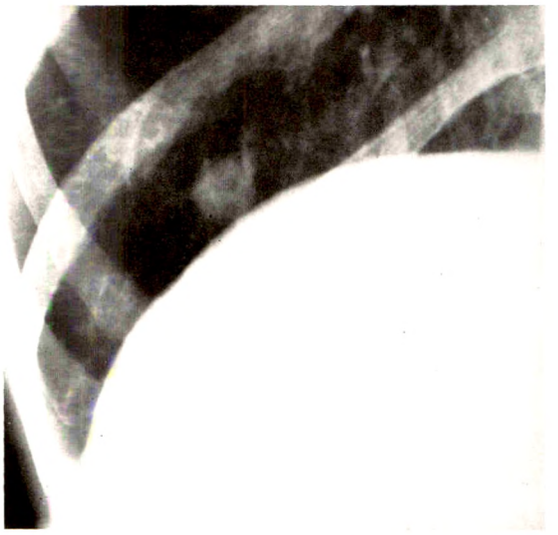


FIG. 3. Magnified view of roentgenogram showing detail of metastatic nodule above right hemidiaphragm in November, 1961, prior to institution of course of chemo-radiotherapy.

DISCUSSION

As pointed out in our previous article, for a reasonable hope of local ablation, a tumor dose of at least 6,000 rads in 6 weeks should be delivered. None of our head and neck cases which received less than this or its time-dose equivalent (6 cases) achieved

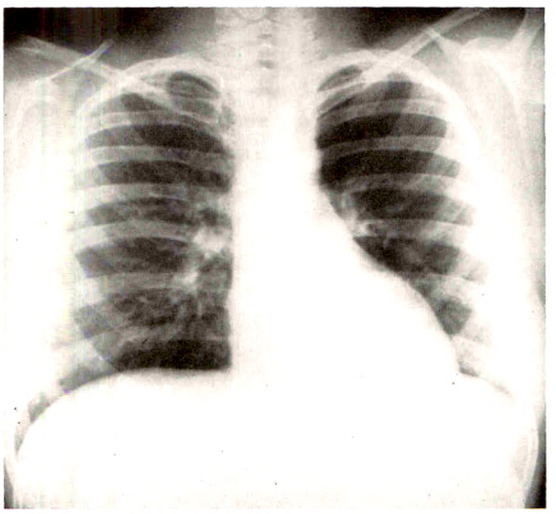


FIG. 4. Chest roentgenogram in August, 1962, showing complete resolution of metastatic nodule and no significant residual pulmonary fibrosis. This is not unusual considering the peripheral nature of the nodule and the small portals employed.

local tumor ablation, while 4 cases treated to this level, did achieve local control. The problems inherent in delivering such a dose to areas other than the head and neck or pelvis are rather obvious and have been previously discussed.

The apparent usual propensity of this tumor for rather early dissemination is probably the single-most important reason for the low long term salvage rate. In general, the head and neck primary lesions have a poor prognosis. Moore and Grossi[8] reported a 5 year survival rate of 8.2 per cent and Stout[13] reported 2 of 15 patients free of disease after 5 years. Lindberg,[6] reporting from the M. D. Anderson Hospital, recorded only 2 of 29 patients free of disease after 5 years, and these were apparently surgical or surgical-chemotherapy cases.

Many writers comment on the high incidence of local recurrence (persistence). In the M. D. Anderson series, local recurrence was noted in 62 per cent of cases. Lindberg also feels that radical radiation therapy (5,000 rads tumor dose) followed by radical surgery is the treatment of choice. In the nasopharynx, this is not readily feasible and, except for the orbit, may be excessively mutilating for the salvage obtained. In a previous series, this author commented upon a minimal predictable tumor dose of 6,000 rads in 6 weeks. If doses less than this are employed, eventual local recurrence (persistence) is the rule. The reported patient received 6,750 rads in slightly less than 6 weeks and permanent local control was achieved. As previously mentioned, one must not be misled by the frequently rapid initial regression of the tumorous mass with transient resolution of symptoms.

In the initial paper, a comment concerning the fact that not all metastases are clinically disseminated would appear to be confirmed by this patient who had a successfully treated, apparently solitary metastatic pulmonary focus. In our original series, 2 other cases were reported who also had isolated, apparently successfully treated, pulmonary lesions.

SUMMARY AND CONCLUSION

A 5 year survivor with no clinical evidence of disease is discussed, who presented in 1961 with a botryoid embryonal rhabdomyosarcoma of the nasopharynx. A combined chemo-radiotherapeutic radical approach was undertaken which has controlled the local disease. Six months later, combined therapy was undertaken for a solitary pulmonary metastasis. Apparently, early metastases are not widely disseminated in all cases, and the presence of a solitary pulmonary lesion should not necessarily preclude ablative local therapy. The plea for radical radiotherapy, 6–7,000 rads in 5 to 7 weeks, is stressed, if local persistence is to be eliminated.

Since embryonal rhabdomyosarcoma can be controlled locally by radical radiotherapy, it is felt to be the treatment of choice in lesions which do not readily lend themselves to complete en bloc surgical extirpation. Certainly, the treatment plans which employ chemotherapy (*i.e.* actinomycin D or vincristine) and radiotherapy, deserve further exploration, as do pre-planned preoperative radiotherapy-surgical combinations in sites more amenable to radical surgical attack.

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THE EFFECTS OF IRRADIATION (EXTERNAL AND INTERNAL) ON LYMPHATIC DYNAMICS*

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THIS report details the alterations in lymphatic dynamics which occur following the administration of external and internal irradiation to the lymphatic system. Studies were performed to note the effect of various types of external irradiation (orthovoltage and supervoltage), and internal irradiation (intralymphatically administered radioactive isotopes) upon the lymph nodes, the lymphatic vessels, and upon lymphatic dynamics. Lymphographic studies were performed in a series of 30 patients exposed to either external or internal irradiation.

METHODS AND MATERIALS

As previously described,[1] a modification of the technique of Kinmonth[6] was used in this investigation. Briefly, the lymphatic vessel of a hand or foot was identified by the intradermal injection into an intermetacarpal or intermetatarsal web space of 1.5 ml. of an 11.0 per cent aqueous solution of the blue dye, alphazurine 2 G. Shortly thereafter, nonradioactive ethiodol was injected into the cannulized lymphatic vessel.

Three isotopes were employed for internal irradiation. In most instances, radioactive ethiodol (I^{131} ethiodol)* was used, wherein much of the stable I^{127} has been replaced by a radioactive I^{131} atom. In other instances, either radioactive gold (Au^{198}), or radioactive yttrium 90 (Y^{90}) micromicrospheres† were used. At the completion of the endolymphatic injection, the wound was carefully cleansed with 1,000 cc. of normal saline solution which assured the washing away of possible residual radioactivity, and the wound was closed with interrupted 3–0 dermalon sutures.

Roentgenograms of the pelvis, abdomen and extremities immediately after the intralymphatic injection of the radiopaque ethiodol permitted the visualization of the lymphatic system and provided an index of its form and function. Normally, the lymphatic vessels will have cleared themselves from the injected contrast medium within 24 hours. Accordingly, roentgenograms taken 24 hours after the endolymphatic injection of ethiodol provide a basis for an evaluation of the functional capabilities of the lymphatic vessels. Incomplete emptying of the lymphatic vessels after 24 hours would be indicative of defective lymphatic flow. On the other hand, ethiodol normally remains within the lymph nodes for many months.

In 10 patients, the lymphographic studies were performed after the administration of external radiation therapy; in 20 patients the studies were performed after the endolymphatic administration of radioactive isotopes. In the latter group, the internal irradiation was given in an effort to control certain primary malignant neoplasms of the lymph nodes (malignant lymphomas), as well as occult metastases in the lymph nodes, as reported in another paper of this series.[2]

* Ethiodol is the registered trade name of E. Fougera & Co., Hicksville, N.Y.; made radioactive and supplied by Abbott Laboratories, North Chicago, Ill.

† Supplied by 3M Company, St. Paul, Minn.

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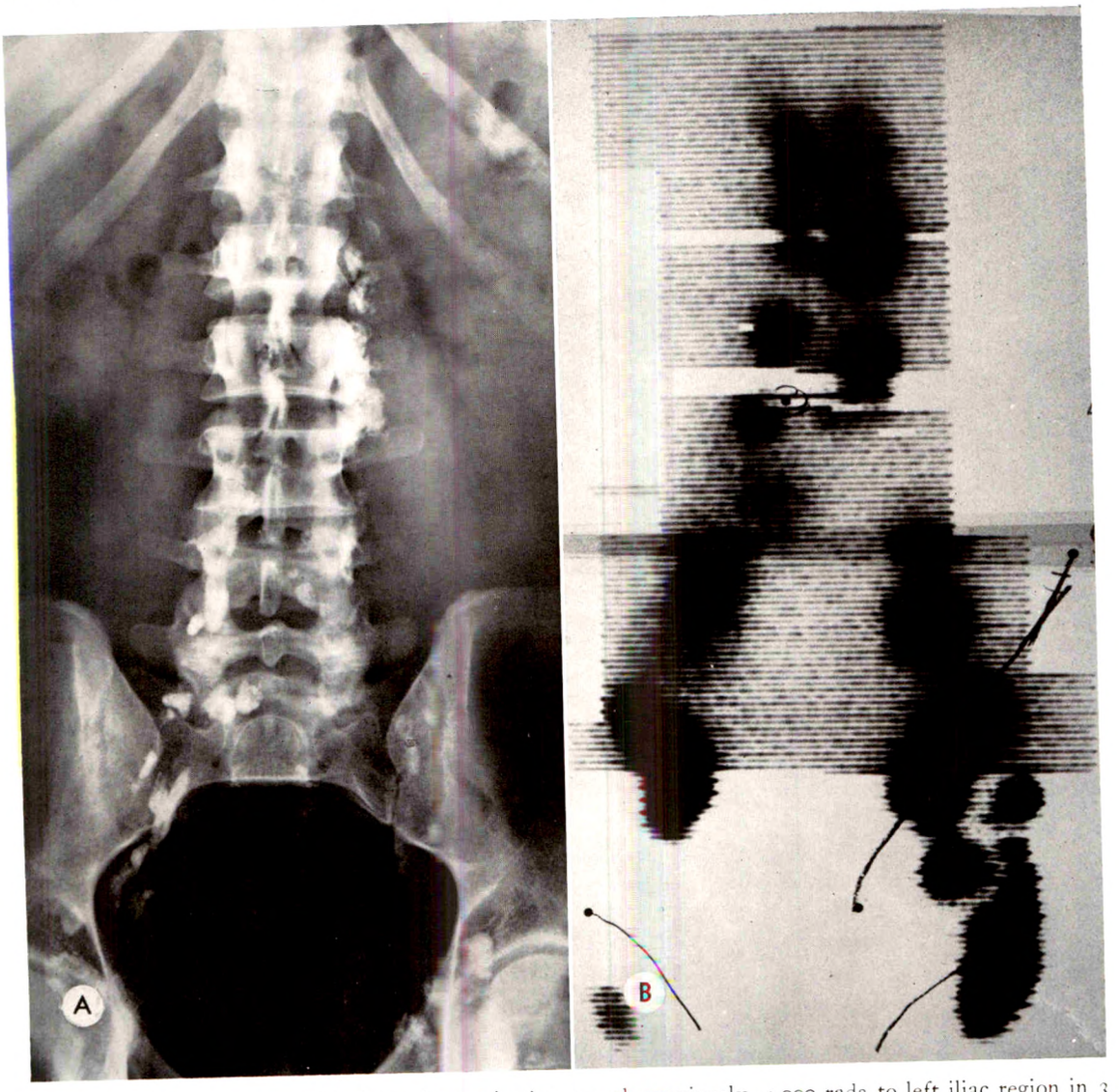


FIG. 1. (*A*) Lymphogram of patient who received, 1 month previously, 4,000 rads to left iliac region in 3 weeks from a Co^{60} teletherapy unit. Note diminished number and small sized lymph nodes in left pelvic region. No alteration in lymphatic dynamics exists as the periaortic lymph nodes in the left side fill well with the ethiodol. (*B*) Scintiscan after administration of I^{131} ethiodol. Note retention of the isotope throughout the pelvic and periaortic lymph nodes.

RESULTS

THE EFFECT OF EXTERNAL RADIATION THERAPY UPON LYMPHATIC DYNAMICS

Of the 10 patients who received external irradiation, none manifested any alteration in lymphatic dynamics. In each instance the lymphatic system emptied of the injected ethiodol within 24 hours, and the lymphatic vessels appeared normal.

Figure 1*A* is a lymphogram of a 32 year old male who received 4,000 rads to the left iliac and inguinal region in 23 days from a Co^{60} teletherapy unit for the treatment of possible metastases from a primary testicular cancer. It should be noted that the lymph nodes have been largely destroyed by the external irradiation, but there is free flow of the ethiodol throughout the lymphatic system in the pelvic and abdominal regions. This is demonstrated on

the left side; however, on the right side where no irradiation had been given, the lymph nodes are larger and more numerous. A scintiscan of this patient indicates a retention of the radioactivity within the remaining lymph nodes on the left side, as well as in the periaortic lymph nodes (Fig. 1*B*). There is, of course, an abundant retention of radioactivity on the right side where no previous external radiation therapy had been given.

This patient demonstrated no defect in the physiology of the lymphatic system subsequent to a therapeutic dose of Co^{60} teletherapy. Whereas a significant difference is manifest in the size and number of the lymph nodes on each side, there has been no compromise in lymphatic dynamics. Furthermore, the retained radioactivity throughout the entire lymphatic system subsequent to external radiation therapy may be useful as a means for the possible sterilization of any residual cancer cells present. These observations regarding isotopic retention following external irradiation are similar to those made by Dettman, King, and Zimberg.[4]

Figure 2, *A* and *B*, represents the lymphograms of a 64 year old male who received 3,000 rads external irradiation in 3 weeks to the pelvic region and abdomen from a 250 kv. generator, 1 year before the lymphographic study. He suffered from generalized lymphosarcoma for which a resection of the small intestine had been performed because of an intussusception produced by the lymphosarcomatous process. In this patient, the lymph nodes are fewer in number than normally seen, but the lymphatic vessels are clearly visualized and demonstrate that they are capable of delivering the injected medium throughout the pelvis and into the retroperitoneal lymph nodes. The lymphatic vessels appear normal and even the smallest vessels are functional, transporting the administered contrast material. In this instance, radioactive ethiodol was used to provide continued irradiation to the residual retroperitoneal and pelvic lymph nodes.

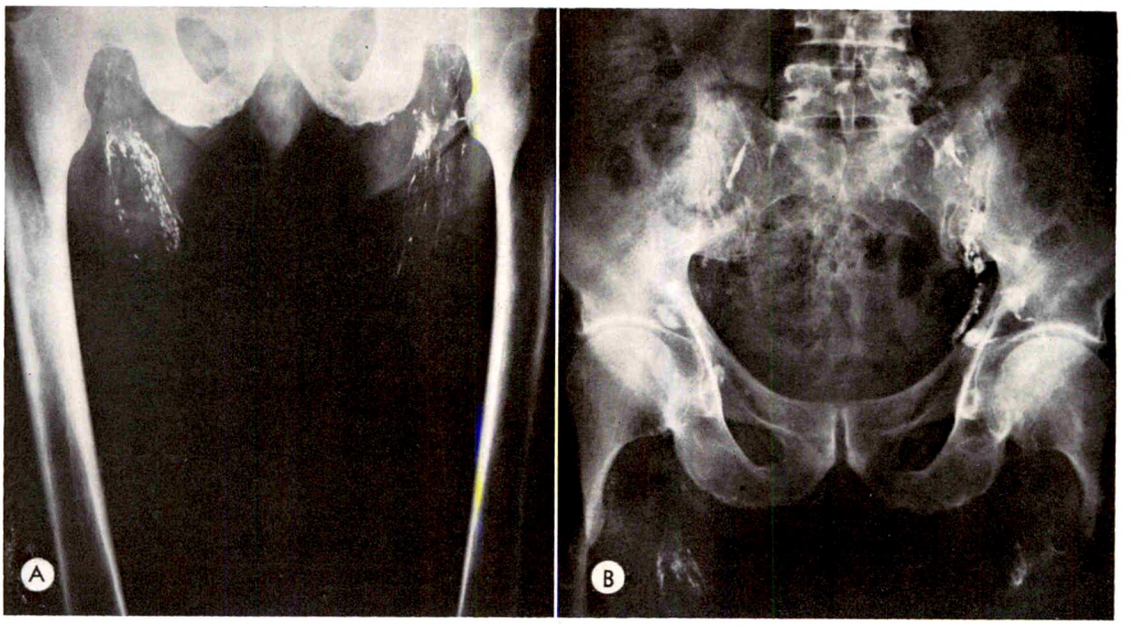


FIG. 2. Lymphogram of patient with lymphosarcoma who received 3,000 rads in 3 weeks, 1 year prelymphographic study. (*A*) Note complete emptying of peripheral lymphatic vessels in 24 hours. This is normal. In the presence of obstruction, retained ethiodol may remain in these vessels for weeks and months. (*B*) Observe small size of the lymph nodes with no interference in functional capacity of the lymphatic vessels.

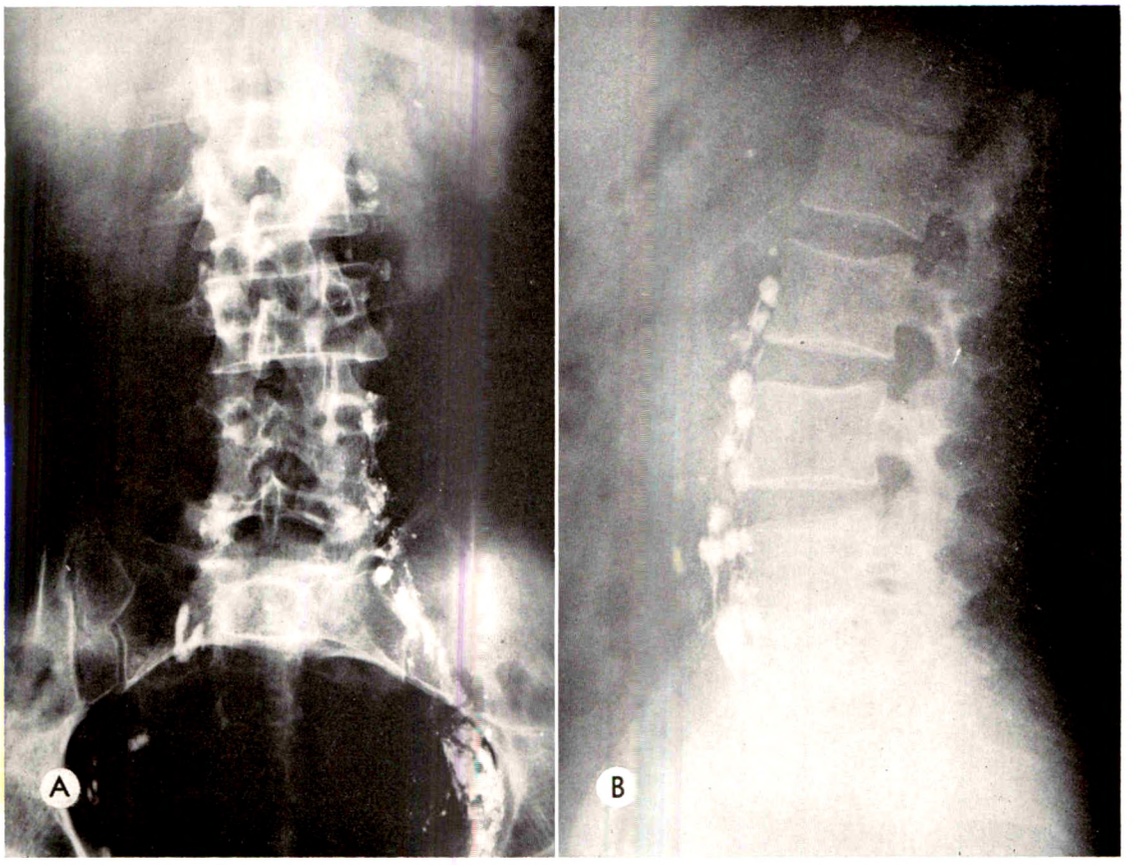


Fig. 3. (*A*) Anteroposterior and (*B*) lateral lymphograms made 6 months after a course of supervoltage roentgen therapy (see text for factors). Note residual lymph nodes and the functional capacity of the lymphatic vessels.

This patient demonstrates the functional capacity of the lymphatic system of the pelvis after the administration of 3,000 rads in 2 weeks to the entire lower abdomen, given 1 year before the isotopic lymphogram. The lymph nodes are smaller and fewer in number than normally present, indicating the effect of the external radiation therapy.

Figure 3, *A* and *B*, shows the lymphograms of a 45 year old male who had a testicle removed for a seminoma. Six months before the performance of isotopic lymphography, he was given supervoltage radiation therapy with a 2 million volt generator. The positions of the external radiation treatment portals are indicated in Figure 4. The first course of irradiation was directed to the right iliac lymph nodes

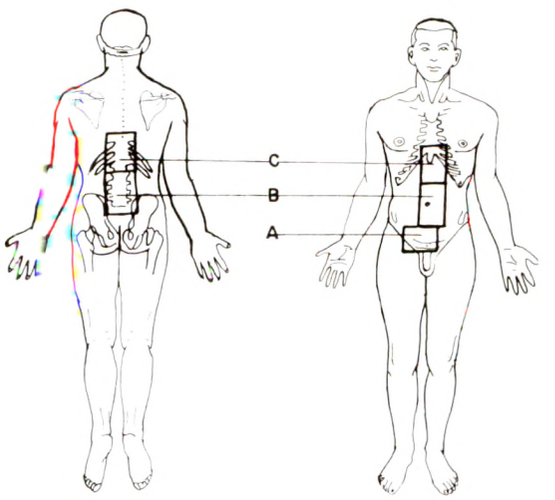


Fig. 4. Positions of external irradiation portals of patient in Figure 3, *A* and *B*.

through a single anterior portal (A); the tumor dose delivered was 2,875 rads in 8 days. The second course was delivered to the prelumbar lymph nodes through anterior and posterior portals (B), each measuring 10×15 cm. and a tumor dose of 2,016 rads in 10 days was delivered. The third course of irradiation was directed to the lymph nodes at the epigastric level using a similar technique (C). A total tumor dose of 2,120 rads was delivered to the epigastric lymph nodes in 10 days.

The lymphograms (Fig. 3, *A* and *B*) demonstrate that the lymph nodes of the right pelvic region have been partially destroyed. A significant number of lymph nodes in the left pelvis and abdomen persist and are visualized up to the level of the second lumbar vertebra, despite a rather large dose of external irradiation. The external irradiation in no way interfered with the transport of the administered ethiodol, given in the form of radioactive I^{131} ethiodol (28 mc) to supplement the external radiation therapy.

In this instance, the effect of supervoltage irradiation to the lymph nodes and lymphatic vessels of the pelvis and abdomen is demonstrated. Despite the rather large dose of external irradiation, functional lymph nodes persist in the abdomen. However, the external irradiation exerted no apparent effect upon the transport capacity of the lymphatic vessels. The peripheral lymphatic vessels of the lower extremities were clear of the contrast medium within 24 hours, a situation which occurs in a normal individual.

Figure 5, *A-D*, shows the lymphograms of a 55 year old woman with Hodgkin's disease. Surgical excision of 1 lymph node was followed by a course of Co^{60} teletherapy equaling 3,000 rads in 3 weeks to the right groin, given 1 year before the lymphographic studies.

The lymphograms demonstrate neither defect in, nor interference with, the normal sequence of the endolymphatically administered ethiodol. Figure 5*A*, taken immediately after the ethiodol administration, reveals a rather rapid transport of the contrast material to the pelvic lymph nodes on the right side (site of previous irradiation), whereas none has entered the lymph nodes of the left side. Figure 5*B* demonstrates the lymphatic vessels of the right thigh to be of better caliber in comparison to those of the left side. In this instance, the complete emptying of the distal lymphatic vessels of the extremities should be noted. Figure 5*C*, made 5 days after *A* and *B*, shows enlarged and functional lymph nodes on both sides of the pelvis, and no effect from the prior external irradiation can be discerned. Figure 5*D* shows the enlarged lymph nodes of Hodgkin's disease extending into the periaortic level.

This patient with Hodgkin's disease demonstrates the inefficacy of external irradiation (in the dose given) to destroy the lymph nodes. The lymphatic vessels appear normal in size and number and are active in the transport of the administered ethiodol (which cleared from the lower extremities within 24 hours). The integrity of the functional capacity of the lymphatic vessels has not been compromised.

THE EFFECT OF INTERNAL RADIATION THERAPY UPON LYMPHATIC DYNAMICS

A series of 20 patients was treated by the endolymphatic administration of various radioactive isotopes. Being both radioopaque and radioactive, I^{131} ethiodol thereby serves a dual function. Studies made on excised lymph nodes after the endolymphatic administration of 20 to 35 mc I^{131} ethiodol demonstrated the deliverance of doses varying from 20,000 to 50,000 rads to the lymph nodes during the biologic activity of this nuclide. This isotope was used chiefly in those patients suffering from disseminated malignant lymphoma in an effort to irradiate the pelvic and retroperitoneal lymph nodes. Two other isotopes were utilized: (1) radioactive Au^{198} administered intralymphatically as a submicron colloidal suspension, and (2) radioactive Y^{90} micromicrospheres administered in the form of tiny plastic spheres measuring 1 to 4 mi-

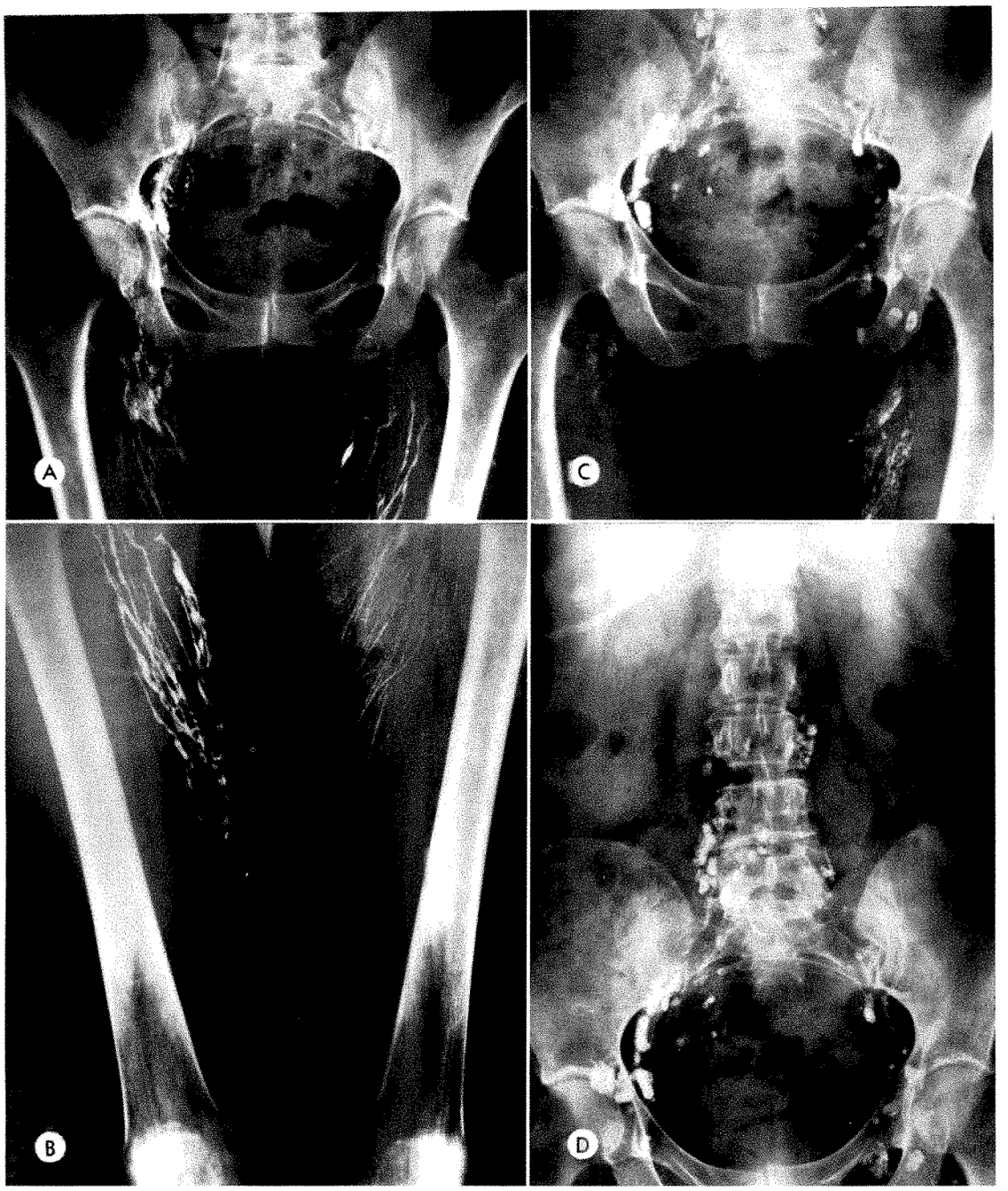


FIG. 5. Lymphograms of a 55 year old female with Hodgkin's disease who received 3,000 rads in 3 weeks to the right groin, 1 year before the lymphographic study. (*A*) Note transport of ethiodol to pelvic lymph nodes on right side (irradiated side) and none to the left pelvic lymph nodes. Apparently, the irradiation enhanced the transport of ethiodol, possibly by destroying a number of the pelvic lymph nodes. (*B*) Right lymphatic vessels (irradiated) are more dilated than those on the nonirradiated left side. (*C*) Lymphogram 5 days later demonstrating functional lymph nodes and lymphatic vessels on both sides of the pelvis. Note almost complete emptying of the lymphatic vessels of the groin on the irradiated side (right). (*D*) Lymphogram taken same time as *C* showing transport of ethiodol to the periaortic lymph nodes.

crons in diameter, to which the isotope is attached and permanently bound. The Y^{90} was given in conjunction with nonradioactive ethiodol in the hope that the isotope would be filtered by the first echelon of lymph nodes in an effort to provide irradiation to them. This was done for patients harboring occult malignant melanomatous deposits in an effort to irradiate the femoral and inguinal lymph nodes. Studies of the excised lymph nodes after the administration of the Y^{90} demonstrated that the micromicrospheres were concentrated within the femoral and inguinal lymph nodes and that none was noted in the iliac lymph nodes. In contrast, colloidal Au^{198} is transported to the periaortic lymph nodes.

Figure 6, *A*, *B* and *C*, is a series of lymphograms of a 30 year old female with extensive retroperitoneal lymphosarcoma. The diagnosis was made at the time of ex-

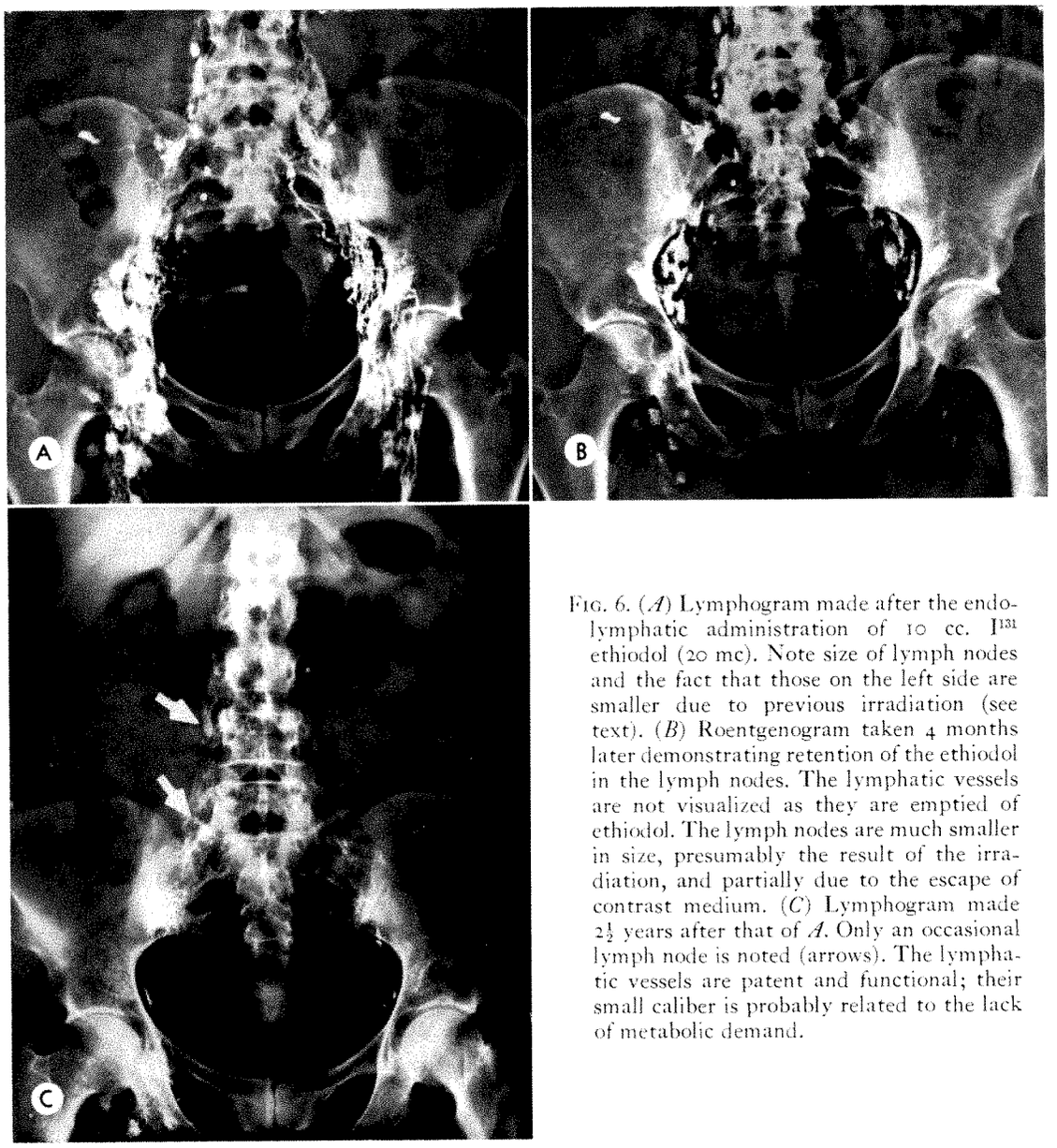


FIG. 6. (*A*) Lymphogram made after the endolymphatic administration of 10 cc. I^{131} ethiodol (20 mc). Note size of lymph nodes and the fact that those on the left side are smaller due to previous irradiation (see text). (*B*) Roentgenogram taken 4 months later demonstrating retention of the ethiodol in the lymph nodes. The lymphatic vessels are not visualized as they are emptied of ethiodol. The lymph nodes are much smaller in size, presumably the result of the irradiation, and partially due to the escape of contrast medium. (*C*) Lymphogram made $2\frac{1}{2}$ years after that of *A*. Only an occasional lymph node is noted (arrows). The lymphatic vessels are patent and functional; their small caliber is probably related to the lack of metabolic demand.

ploratory laparotomy by Drs. George Nagamatsu and Henry P. Leis, who performed the operation because of roentgenographic evidence of an abnormal kidney on the left side. The operation revealed extensive retroperitoneal lymphosarcoma, established by biopsy of one of the excised masses. She was treated initially by the endolymphatic administration of 20 mc Y^{90} into the lymphatic vessel of the left foot. It is estimated that 20,000 rads was delivered to the femoral and inguinal lymph nodes. Figure 6*A* is a lymphogram made 6 months later, at which time 20 mc of I^{131} ethiodol was administered in an effort to irradiate the retroperitoneal lymph nodes and to offer additional irradiation to the pelvic lymph nodes. The functional capacity of the lymphatics is demonstrated, and the internal irradiation of the left femoral and inguinal lymphatic vessels has resulted in a diminution in number and size of the lymph nodes. Figure 6*B* is a lymphogram taken 4 months later; the ethiodol remains in the lymph nodes which are now much smaller in size. Figure 6*C* is a lymphogram made on a routine check-up because of mild symptoms referable to her abdomen and performed 2½ years after the initial endolymphatic administration of ethiodol. One enlarged lymph node is noted, which could presumably be active lymphosarcoma. Note the free transport of the ethiodol throughout the region under investigation. There has been no compromise in lymphatic dynamics. Although the lymph nodes are fewer in number and smaller in size than normal (the result of previous irradiation), the lymphatic vessels are functioning normally. The contrast material emptied itself from the lymphatic vessels of the leg within 24 hours, demonstrating no interference with the normal transport of the administered contrast medium subsequent to the internal irradiation. This patient received an estimated total dose of 50,000 to 80,000 rads to the left femoral and inguinal lymph nodes (20,000 rads from the Y^{90} and 40,000 to 50,000 rads from the I^{131} ethiodol); the dose delivered to the right side was less because only I^{131} ethiodol was administered to both sides. The patient is well and asymptomatic 4 years after the initial therapy; her only symptoms are those referable to a mild hypothyroidism, easily controlled with cytomel.

This is an example of relatively normal lymphatic dynamics in a patient who was given large doses of internal irradiation in the form of endolymphatically administered radioactive isotopes.

DISCUSSION

The effect of radiation therapy upon the lymph nodes and the lymphatic vessels is of the utmost importance, inasmuch as oftentimes the irradiation is administered in an effort to destroy metastases in the lymph nodes. Furthermore, sometimes radiation therapy is given (particularly preoperatively) in an effort to "seal-off the lymphatics" in the hope of preventing spread of the cancer. Our data, gleaned from the lymphographic studies in patients who received either external or internal irradiation, demonstrated very little, if any, effect exerted upon the lymphatic vessels and the dynamics of lymph flow. In contrast, marked effects were noted upon the lymph nodes. This is not surprising, inasmuch as the lymph nodes represent a separate system from that of the lymphatic vessels as emphasized by Herman, Benninghoff, and Schwartz.[5] These authors stress that the lymph nodes arise from an altogether different embryologic vestige than do the lymphatic vessels and are concerned with immune reactions and filtration, in contrast to the function of the lymphatic vessels which is largely for the transport of protein from the gut through the thoracic duct into the systemic circulation, as well as to act as an intermediary between the vascular tree and the cells of the body. The lymphatic vessels are ubiquitous, in contrast to the lymph nodes which are located in specific regions of the body. Accordingly, it is not unusual for these two parts of the lymphatic system to manifest different de-

grees of sensitivity to external and internal irradiation; the lymph nodes composed chiefly of radiosensitive cells manifest a type of reaction to irradiation apart from that of the lymphatic vessels which may be considered a part of the blood vascular compartment. In fact, in lower animals (amphibians) the lymphatic vessels transport blood as well.

One of us (I.M.A.), in 1938 at the Rochester School of Medicine, demonstrated in modified rabbit ear windows that, after an implantation of a Brown-Pearce rabbit epithelioma, there would be an ingrowth of solid endothelial tubes from the surrounding tissue into the Brown-Pearce tumor. Most of these endothelial tubes differentiated into single endothelial cellular layer-lined blood vessels, and some were shown to transport lymph. Following radiation therapy, it was shown that a free flow of blood occurred, and that the erythematous state was related to an increased blood flow as well as to an escape of blood cells from these very sensitive endothelial-lined tubes. Very large doses of irradiation were necessary to produce any effect upon the lymphatic vessels.

Van den Brenk,[8] studying the effect of irradiation from a Co^{60} source in a Sandison Clark type ear chamber in rabbits, demonstrated that the lymphatics survived after a dose of at least 4,000 gamma roentgens; that irradiation does not induce endothelial swelling sufficient to cause any blockage in the lumen of the lymphatic vessels. Doses in excess of 5,000 gamma rads result in the destruction of the lymphatic vessels, which is due to cellular disintegration and endothelial "rupture." The author further demonstrated that the reaction of the irradiated preformed lymphatic vessels to a series of vasotropic drugs revealed no alteration in response from the normal lymphatics. The effect of irradiation upon the lymphatic vessels differs from the effect of bacterial infection or mechanical trauma, which cause an intense lymphatic regeneration.

Lenzi and Bassani[7] studied the effect of 200 kv. irradiation, Co^{60} teletherapy, and a 15 mev. betatron on the lymphatic vessels of rabbits and guinea pigs, as well as on human uteri. These authors demonstrated that an interruption in lymphatic flow does not occur from the doses of irradiation ordinarily given. An interruption in the lymphatic network occurs only in regions of necrosis, and even there it requires a dose of about 20,000 rads. They showed that in uterine tissue which had received between 12,000 and 15,000 rads and where neoplastic cells could not be identified, it was impossible to interrupt the normal lymphatic structures.

More recently, Dettman, King, and Zimberg[4] studied the effect of irradiation and surgery on lymph node function in rabbits. They used colloidal gold 198, injected into the posterior foot pad of the hind limb of dogs, and administered varying doses of irradiation to note its effect on the localization of the radioactive material. They observed that all of the radioactive gold, so administered, would localize in the popliteal lymph node. Even after excision of the popliteal lymph node, much of the radioactive gold localized at the site of excision, but in about 1 month lymphatic continuity had been reestablished and the isotope then localized in the abdominal lymph nodes. They also observed that after the administration of 2,000 rads to the popliteal lymph node with orthovoltage roentgen irradiation, no effect in the pickup of the gold was manifested. However, after the administration of 6,000 rads, starting 2 months after the irradiation, some of the gold reached the abdominal lymph nodes, demonstrating the lack of filtration by the popliteal lymph node. After the administration of 10,000 rads, the distribution of the gold was the same as in the controls. They believed this to be due to the fibrosis which occurred in the irradiated region. They conclude, "that the irradiation did not entirely eliminate the localization of colloidal gold in the popliteal lymph node

site in any case," and they postulate that with particles as large as cancer cells, no alteration would be noted.

COMPARISON OF THE EFFECTS OF SURGERY AND IRRADIATION UPON THE LYMPHATIC VESSELS

The authors have demonstrated the effect of surgery upon lymphatic dynamics.[3] Briefly, these changes are:

1. Following either a radical groin or axillary dissection, certain alterations in lymphatic dynamics occur. There is an extensive escape of lymph through the severed lymphatics, resulting in the formation of a lymphocele. Also, as a result of severance of the communicating lymphatic channels, there is an escape of lymph and cancer cells into the free tissue spaces where the cancer cells may "seed" and grow, presenting as metastases.

2. A sealing-off of the severed lymphatic vessels occurring at the incisional site hinders and obstructs lymphatic flow with the development of the following sequence of events:

(a) There is resultant retention of lymph in those lymphatic vessels distal to the operative site, producing a stagnant state.

(b) The blocked lymphatic vessels may form collateral channels with adjacent lymphatic vessels, with the subsequent reestablishment of lymphatic flow.

(c) Due to lymphatic blockage, and in the presence of an inadequate development of collateral circulation, a regurgitation of lymph occurs within the subsequently functional superficial or dermal lymphatic channels. As a result, edema of the extremity may occur.

It is thus demonstrated that the surgical extirpation of lymph nodes is not without hazard, particularly when the operation is done in a discontinuous manner. External and internal radiation therapy, apparently when given in the dose range described herein, exert no demonstrable effect upon lymphatic dynamics. Irradiation does not cause blockage of lymphatic flow, nor does it result in the formation of collateral lymphatic channels for possible dissemination of cancer cells throughout the body. Even after the administration of therapeutic doses of irradiation, the filtration stability of the residual lymph nodes seems to be intact.

The presence of certain lymph nodes in the irradiated regions may be the result of either a resistance of these lymph nodes to the irradiation, or a regeneration of the lymph nodes from those cells not destroyed by the irradiation. The observation has been made that when lymph nodes are incompletely excised, a regeneration of the lymph node will occur from this nidus of lymphatic tissue. A similar situation probably prevails for the effect of irradiation, in that the residual lymphatic tissue acts as a focus from which regeneration can occur.

Van den Brenk[8] demonstrated that the lymphatics were not observed to regenerate in the repair blastema when a dose of irradiation higher than 2,000 gamma roentgens was administered; a single dose of 1,000 gamma roentgens permitted their normal regeneration. This observation might be pertinent to the effect of combined surgery and irradiation in establishing the continuity of the lymphatic vessels.

SUMMARY AND CONCLUSIONS

1. Of the 10 patients on whom lymphographic studies were made after the administration of external radiation therapy, none manifested abnormality or compromise in lymphatic dynamics. Of the 20 patients on whom lymphographic studies were made after the endolymphatic administration of radioactive isotopes very little, if any, effect was observed upon the lymphatic vessels and the dynamics of lymph flow; however, a marked effect upon the lymph nodes occurred.

2. Whereas the lymph nodes are radiosensitive and can be destroyed with the usual doses of external and internal irradiation given in clinical practice, the lymphatic vessels are radioresistant and orthodox dosages exert no observed effect upon them

as noted in this study. Attention is directed to the fact that the lymphatic vessels should be considered separately from the lymph nodes in that they are different organs structurally and functionally.

3. The free transport of administered ethiodol through irradiated regions was observed. No new collateral lymphatic vessels were seen and no obstructive phenomena in the lymphatic system occurred. Accordingly, the concept whereby irradiation would seal off the lymphatic vessels appears to be incorrect.

4. A comparison is made of the effect of surgical extirpation of certain groups of lymph nodes (lymph nodes in the groin and axilla) with the effect of irradiation of these lymph nodes.

5. The alterations in lymphatic dynamics which occur after surgery are profound, and demonstrate that if clinically indicated, a radical excision of the lymph nodes should be performed in continuity with the primary cancer. If an in continuity operation cannot be performed and if one is dealing with a radiosensitive malignant neoplasm, irradiation might be the preferred treatment in that it does not significantly alter the lymphatic dynamics.

6. No significant change in lymphatic vessel structure and function was observed either from irradiation delivered from an external source, or from that administered internally in the form of the endolymphatic injection of radioactive isotopes (I^{131} ethiodol, Au^{198} and Y^{90} micromicrospheres).

7. The clinical implications of the foregoing observations are discussed.

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THE VALUE OF STRONTIUM 85 BONE SCANNING IN RADIATION THERAPY*

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THERE is general agreement that a need exists for new techniques to determine the presence and location of tumor metastasis to bone. It is often not sufficient to know that a patient has had cancer; it is necessary to know, also, that the present symptoms of which the patient complains are also due to cancer. It may be justified to go to considerable lengths to make such a decision. It is then necessary to determine whether the condition should be treated and if so, whether by irradiation or by some other method or combination of methods. Martin *et al.*,[3] in discussing accuracy in radiation therapy, mention the following 3 sources of error in delivering a prescribed dose to a given site—dimensional errors in planning, errors in determination of isodose distribution, and errors in calculation of dose delivered. Error in selection of exact treatment area was not mentioned. In the past, radiation therapists depended upon clinical judgment and roentgenograms to determine the sites of therapy. The purpose of this report is to describe the usefulness of strontium 85 bone scanning as an adjunct in radiation therapy for better management of patients with metastatic bone disease.

Postmortem examinations have demonstrated that 85 per cent of patients dying of the more common types of cancer have bone metastases which in many cases were not visualized by conventional roentgenograms. It has been shown that lesions in vertebrae smaller than 1 cm. in diameter are usually not seen on roentgenograms because 30 to 50 per cent of the bone must be decalcified before a change can be appreciated.

Today, bone scanning with radioactive strontium 85 for detection of tumor metastasis has become an established procedure in many departments of nuclear medicine. Convincing evidence has demonstrated that radioactive strontium 85 is deposited in the vicinity of bone metastasis in quantities sufficient to be delineated by scanning, often before the lesion can be seen on the roentgenogram.[1]

Strontium 85 has many features of an ideal scanning agent. It emits a monoenergetic gamma ray of .513 mev. which is readily collimated by commercially available instrumentation. It has a half-life of 64 days which makes it convenient for administration at almost all times. Strontium 85 follows closely the metabolic pathway of calcium in bone and its deposition reflects alterations in local calcium metabolism to a very high degree. It is injected intravenously in 100 μc doses which are rapidly taken up by bone. Approximately 20 to 40 per cent of the injected dose is deposited in bone[2] and the remainder is excreted in the urine and feces over a considerable period of time, the highest rate of excretion being within the first 24 hours. In the examination of patients with problems below the diaphragm, it is very important to have thorough bowel cleansing because of fecal excretion of strontium.

Our bone biopsy studies of patients with metastatic cancer who have been scanned with radioactive strontium have revealed that radiostrontium deposition occurs in new bone formed in reaction to the presence of tumor.[2] The radiostrontium is deposited in immature osteoid tissue laid down adjacent to the invading malignant cells. Since young osteoid tissue is not yet mineralized enough to be appreciated on a roentgenogram, it is at this stage that we

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
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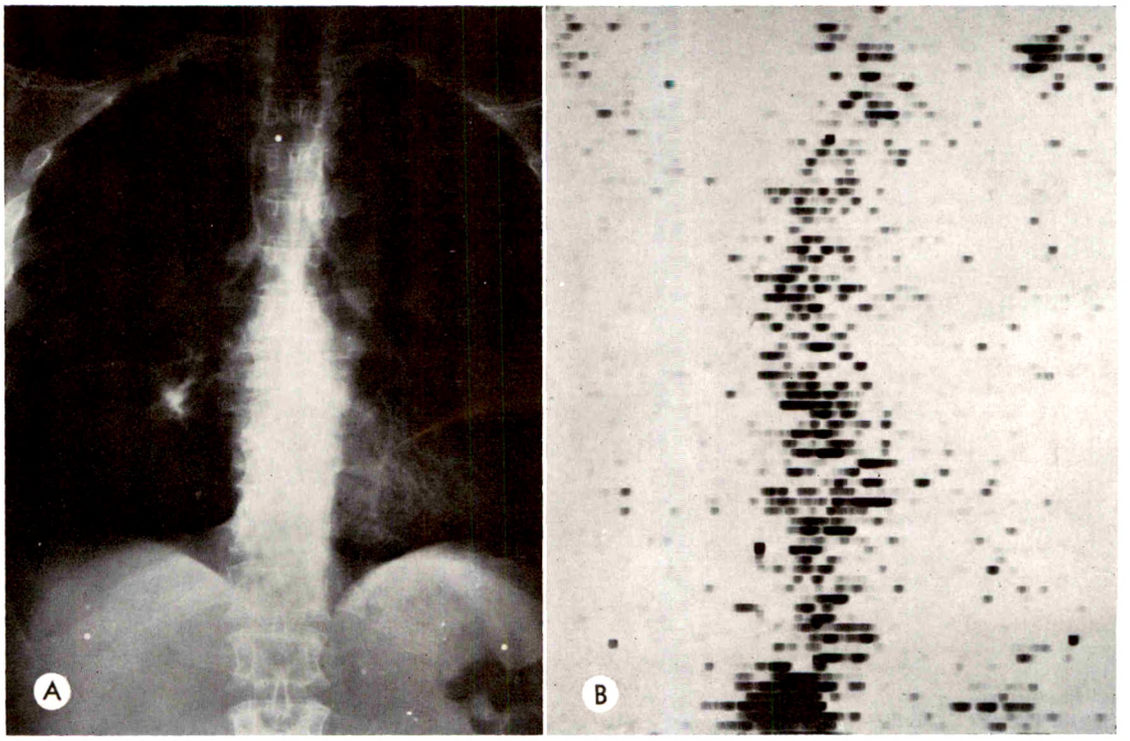


FIG. 1. Case 1. (*A*) Roentgenogram of dorsal and upper lumbar spine shows no evidence of metastasis. (*B*) Scan is definitely positive in the region of the 1st lumbar vertebra.

may find a positive bone scan with no roentgenographic evidence of bone metastasis. Later, as mineralization of the osteoid proceeds, radiodensities appear on the roentgenogram and the bone scan continues to be highly positive. Once calcification is complete, there is relatively little exchange with nonradioactive strontium and although the roentgenogram is dense, a nearly normal bone scan results.

In about 2 per cent of our series, the scan was negative despite the roentgenographic presence of bone lesions. These lesions were almost all radiolucent. In these patients, bone biopsies revealed no evidence of reactive bone formation to the invading tumor, only extensive destruction. In the absence of new bone formation, there is also an absence of deposition of strontium.

The mean radiation dose to bone is approximately 1.6 to 4.6 rads per 100 μc administered.

ILLUSTRATIVE CASES

1. DETERMINATION OF THE PRESENCE OR ABSENCE OF METASTASIS

CASE 1 (Fig. 1, *A* and *B*). H. T., a 63 year old male, was admitted to the hospital with the diagnosis of malignancy of the lung. He complained of pain in the lower back of 2 months' duration. A roentgen examination of the dorsal and lumbar spine and pelvis, including both hip joints, failed to show any evidence of metastasis. However, a scan with radioactive strontium revealed an area of increased uptake in the region of the body of the first lumbar vertebra. The patient was then referred for a course of radiation therapy and at its completion the back pain was completely relieved.

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FIG. 3. Case III. (*A*) Roentgenogram showing metastasis involving the posterior aspect of the 9th rib on the right (arrow). (*B*) Scan indicates the presence of multiple areas of metastatic disease involving the entire dorsolumbar spine.

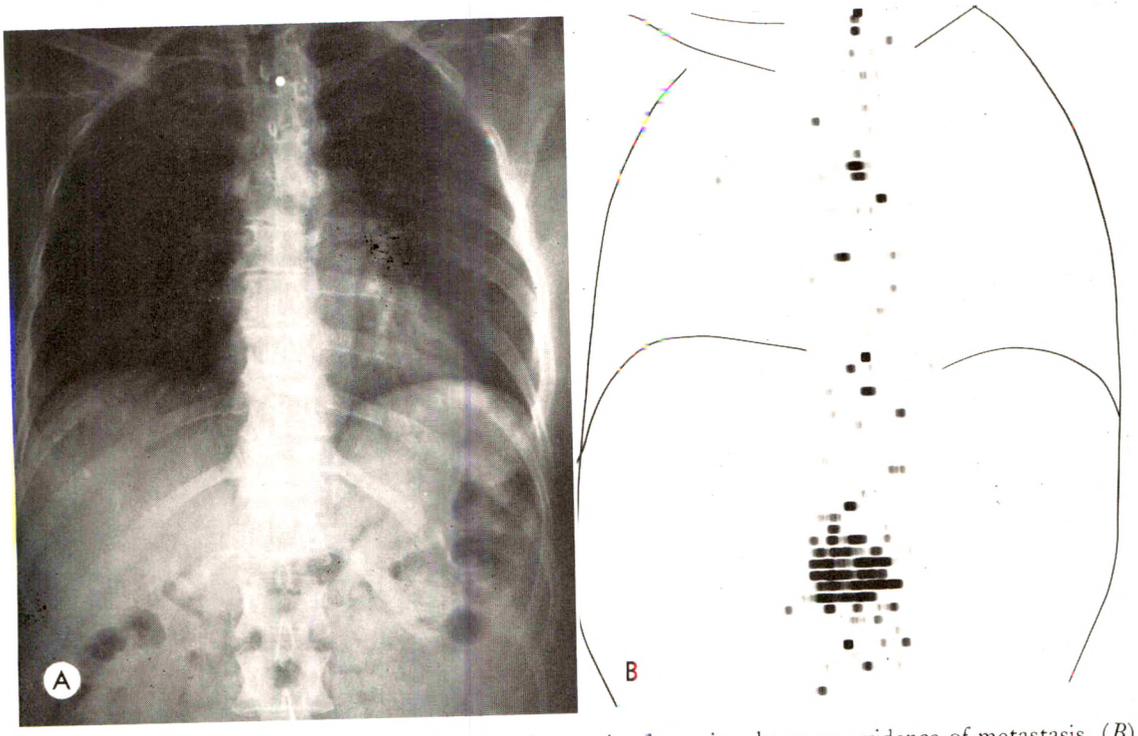
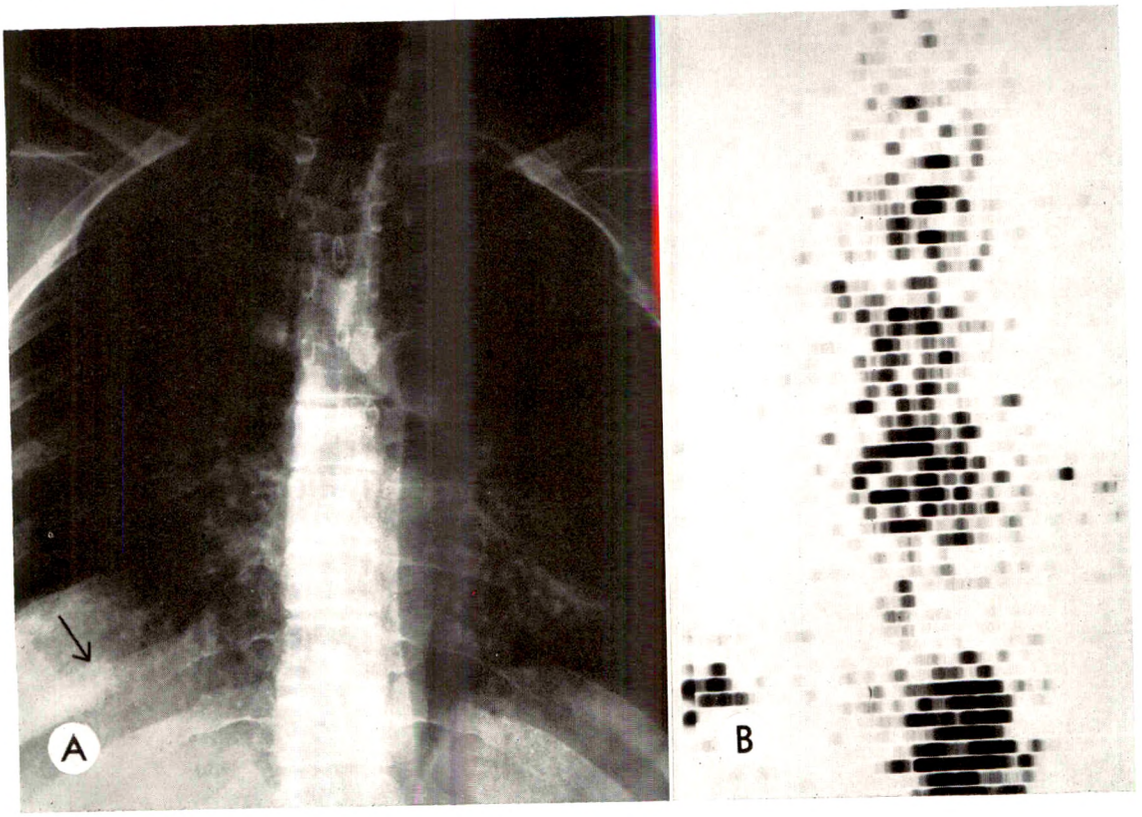


Fig. 2. Case 11. (*A*) Roentgenogram of dorsal and upper lumbar spine shows no evidence of metastasis. (*B*) Scan reveals evidence of metastasis over the body of the 1st lumbar vertebra, in the upper dorsal spine, and in the left upper rib cage.



2. DETERMINATION OF WHETHER DISEASE IS LOCAL OR GENERALIZED

CASE II (Fig. 2, *A* and *B*). F.H., a 48 year old white female, was referred because of pain in her back and a history of a radical mastectomy 1 year previously. Roentgen examinations of the dorsal and lumbar spine and pelvis failed to show any definite evidence of metastasis. A scan with radioactive strontium 85 revealed a "hot spot" over the body of the first lumbar vertebra, in the upper dorsal spine, and in the left upper rib cage.

Comment. In this situation, not only did the scan reveal the presence of metastatic disease, but it indicated that the disease was multifocal in character and that systemic therapy was required in addition to local radiation therapy.

CASE III (Fig. 3, *A* and *B*). M.P., a 51 year old white female, was referred to this department because of pain in the right lower posterior chest wall. The patient had undergone radical mastectomy about 1 year previously. A recent skeletal survey revealed the presence of an osteolytic bone lesion involving the posterior aspect of the 9th rib on the right side. A course of radiation therapy was started to this area and a scan of the skeletal system with radioactive strontium was obtained. This indicated the presence of multiple areas of metastatic disease involving the entire dorsal and lumbar spine which were not discernible on roentgenograms, thus indicating the need for systemic therapy.

3. ACCURATELY LOCATING AREAS REQUIRING THERAPY

CASE IV (Fig. 4). R.K., a 60 year old white female, was treated for carcinoma of the right lung by upper and middle lobectomy. At the time of operation, a right paratracheal lymph node metastasis was found and, accordingly, she was given a course of postoperative cobalt 60 therapy. She remained well until $4\frac{1}{2}$ years later, at which time she complained of pain in the left side of the abdomen of several months' duration. She was admitted to another hospital and intensively studied by means of intravenous urography, barium enema examination, upper gastrointestinal series and roentgenography of the dorsal and lumbar spine. No abnormalities were found in these studies. Following examination in our clinic, a scan was obtained of the dorsal and lumbar spine, which disclosed the presence of areas of increased uptake in the lower dorsal and upper lumbar vertebrae. A diagnosis of metastatic cancer to bone was made. This was felt to be the cause of the radicular pain. A course of cobalt 60 therapy was started, during which a total tissue dose of 2,000 r was administered in 13 elapsed days. Following treatment, the patient reported complete relief of pain.



FIG. 4. Case IV. Scan of dorsolumbar area indicates the presence of metastatic disease in the lower spine.

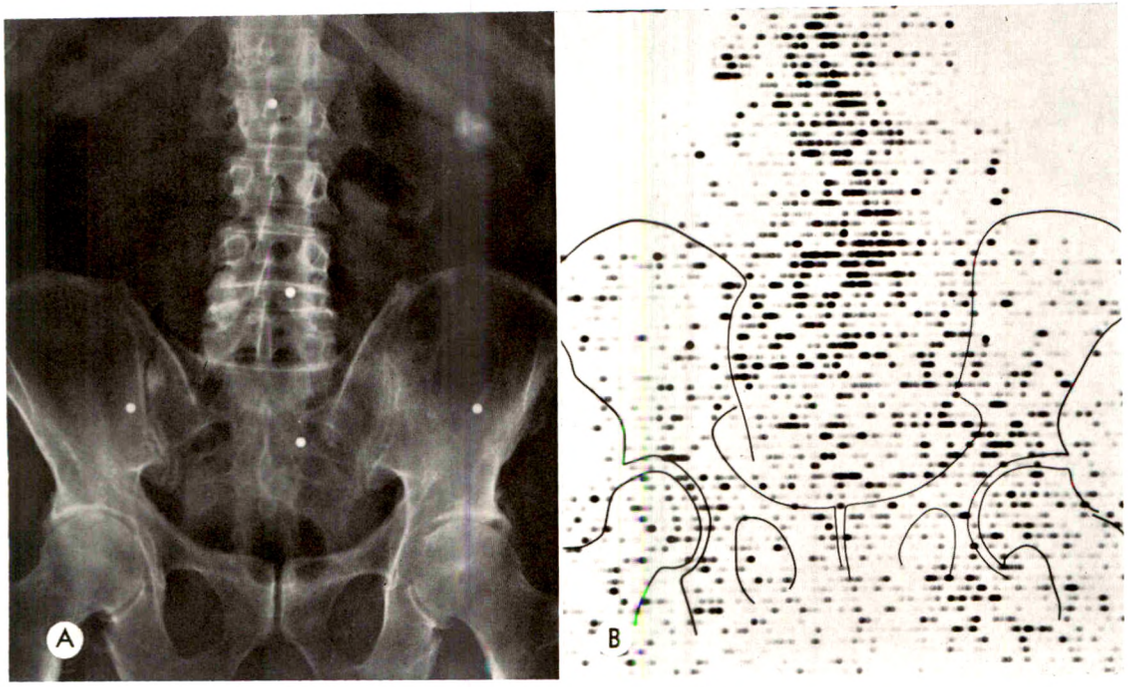


Fig. 5. Case v. (*A*) Roentgenogram of the chest, pelvis and left lower extremity showed no evidence of metastasis. (*B*) The scan indicates the presence of metastatic disease in the lumbar area.

Comment. This case illustrates again the value of the bone scan in disclosing the cause of pain and in directing treatment to the proper site.

Case v (Fig. 5, *A* and *B*). S.U., an 86 year old white male, was admitted to this hospital in April of 1963 with the chief complaint of pain in his left knee of 3 months' duration. The patient was known to have had carcinoma of the prostate gland for about 3 years. Roentgenograms of the chest, pelvis and left lower extremity failed to show any definite evidence of metastasis. A scan with radioactive strontium revealed abnormal deposition in the lower lumbar spine consistent with metastatic cancer, and normal uptake in the extremities. Accordingly, a course of radiation therapy was started to the lumbar spine. Ten days later, at the conclusion of treatment, the patient reported almost complete relief of pain in the knee and was discharged from the hospital.

Comment. Here again is illustrated the value of scanning with radioactive strontium in the diagnosis of metastatic disease as a cause of obscure radicular type of pain.

Case vi (Fig. 6, *A* and *B*). F.A., a 76 year old male, was referred to us with the chief complaint of posterior pelvic, lumbar, hip and leg pain. The patient was known to have carcinoma of the prostate and had been treated with estrogens and bilateral orchiectomy. Roentgen examinations demonstrated widespread metastatic lesions involving the entire skeletal system. In view of the diffuse nature of the bone changes, it was difficult to decide which site to treat with radiation therapy. However, a skeletal scan with radioactive strontium revealed an area of increased uptake in the upper lumbar area and right sacroiliac regions. Accordingly, a course of radiation therapy was instituted to these areas for symptomatic relief.

Comment. In this case, the scan, by delineating areas of active osteogenesis, pointed to the regions requiring radiation therapy for relief of symptoms.

4. To check accuracy of portals

Case vii (Fig. 7, *A* and *B*). S.L., a 74 year old white female, underwent mastectomy in December, 1962. In December of 1965, she complained of severe pain in the right shoulder. Roentgenographic examination failed to demonstrate any evidence of metastasis in this area. However, an abnormal appearance of the body of the 3rd and 4th dorsal vertebrae suggested

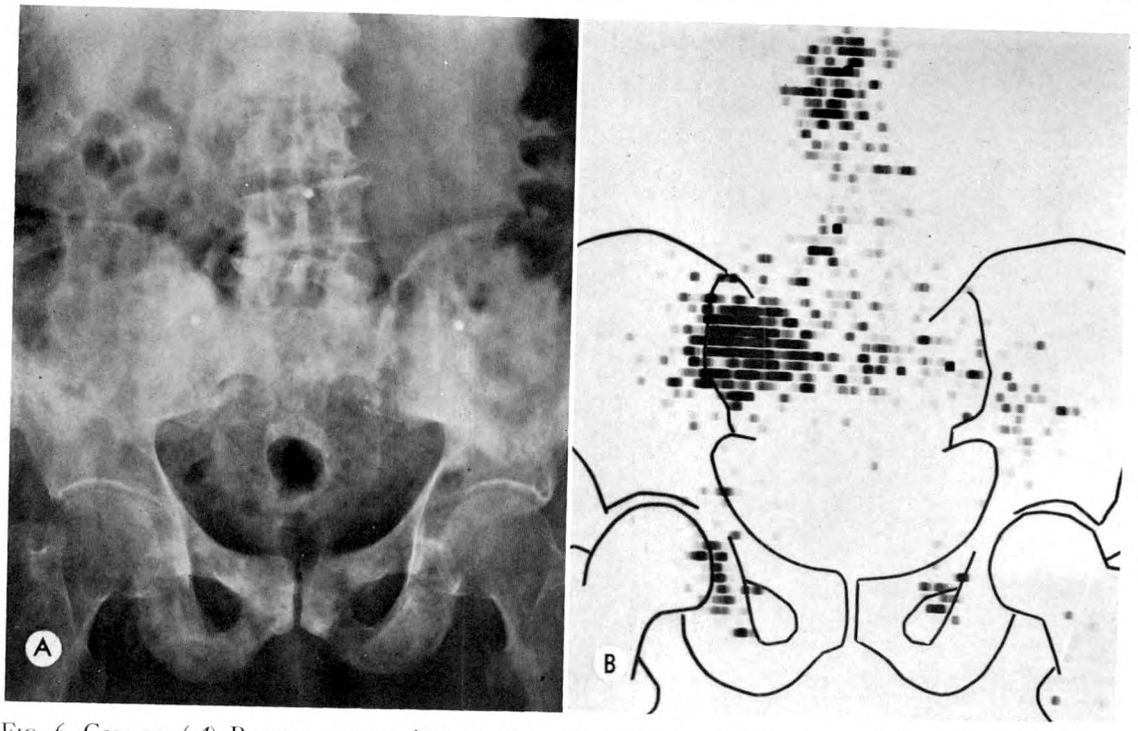


FIG. 6. Case VI. (*A*) Roentgenogram shows widespread metastatic involvement of the pelvic bones. (*B*) Scan reveals areas of increased uptake in the upper lumbar and right sacroiliac region.

the presence of metastasis although there was no indication of local pain at this site. On the basis of the roentgenogram, a course of radiation therapy was started and a radioactive strontium scan was ordered. The scan confirmed the presence of metastatic disease in the spine, but also revealed that the portal outlined did not encompass the entire disease process. The portal was, therefore, adjusted and, at the completion of the course of therapy, the patient reported relief of pain in her shoulder.

Comment. This case is noteworthy because the scan revealed the presence of extensive metastatic bone disease and indicated that the original radiation therapy portal was inadequate. We feel certain that because we were able to adjust the portal properly, a better therapeutic effect was obtained.

5. LOCATION OF A SUITABLE SITE FOR BONE BIOPSY IN A CANCER SUSPECT

CASE VIII. H.K., a 55 year old male, developed pneumonia and back pain due to collapse of D5. Carcinoma was suspected but bronchial washings were negative for tumor. Bone survey roentgenograms of the pelvis were thought to be normal but a strontium 85 scan revealed "hot spots" in the left ilium and right sacroiliac joint. Biopsy of the left iliac lesion showed anaplastic carcinoma.

SUMMARY

Metastasis to bone is a frequent source of pain in patients with cancer, and the response to radiation therapy is often very gratifying. This is especially true if the primary site is the breast, where rapid, complete relief can be obtained in at least 80 per cent of the patients. To obtain maximum benefit, the radiation therapy must be delivered to the exact site which is producing the symptoms. Scanning with strontium 85 has been extremely helpful in obtaining this information. Our experience indicates the usefulness of scanning the skeletal system with strontium 85 in patients suspected of having metastatic bone disease in the following situations:

1. To check the adequacy of treatment portals.

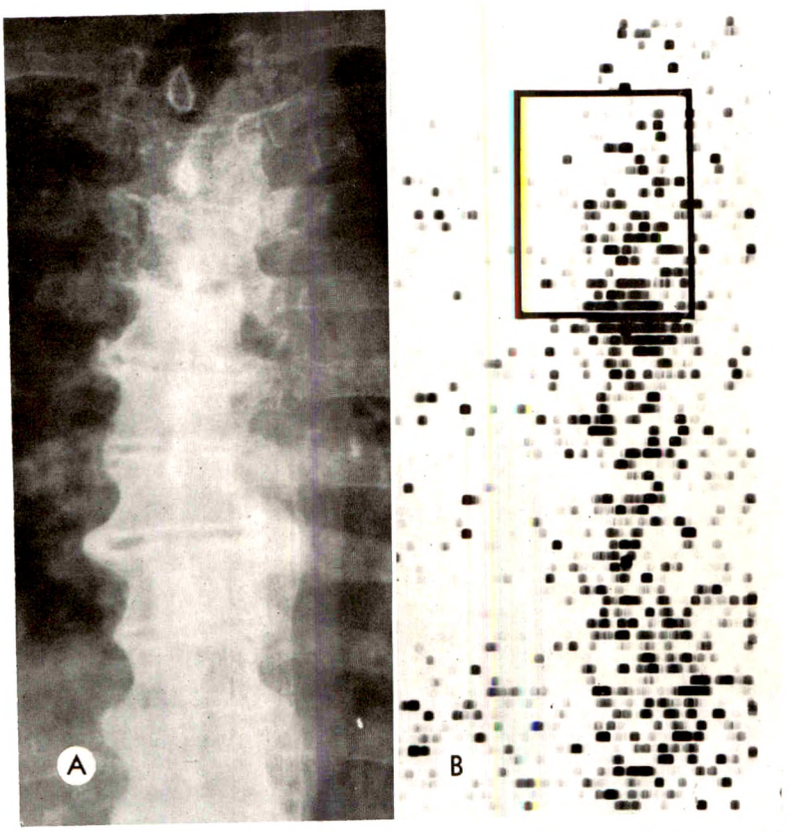


FIG. 7. Case VII. (*A*) Roentgenogram shows no definite evidence of metastatic disease although the appearance of the bodies of the 3rd and 4th dorsal vertebrae are suspicious. (*B*) Scan confirms the presence of metastasis and also indicates that the treatment portals were inadequate. (Reproduced with permission from *Radiologic Clinics of North America*, Dec. 1965, W. B. Saunders Company, Philadelphia, Pa.)

2. To determine whether the disease is localized or generalized in order that appropriate systemic therapy can be given if needed.

3. To locate areas requiring therapy.

4. To locate a suitable site for bone biopsy in order that a histologic diagnosis can be established.

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THE TREATMENT OF BONE METASTASES WITH PARATHORMONE FOLLOWED BY RADIOPHOSPHORUS*

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SINCE the first production of radiophosphorus in the cyclotron in 1934 by Joliot and Curie,[8] this isotope has been widely employed, both as a medical tracer and a therapeutic agent. The first report of the treatment of bone metastases with radiophosphorus was published by Friedell and Storaasli[3] in 1950, when they recorded a case of carcinoma of the breast with disseminated bone metastases controlled for 6 years with re-calcification of the osteolytic lesions. Eight years later, Maxfield and Maxfield[14,15] advised radiophosphorus in combination with androgens to treat osseous metastases from breast cancer.

THEORETIC CONSIDERATIONS

The theoretic bases for the use of radiophosphorus to treat bone metastases are threefold:

1. *Multiplicity of metastatic foci.* Postmortem studies often demonstrate diffuse microscopic lesions which are not visible in the roentgenograms. Therefore, the treatment of choice should be systemic agents rather than a specific local therapy.

2. *Selective localization of radiophosphorus in the skeletal system.* Animal studies demonstrated the deposition of radiophosphorus to be higher in bone than in liver and other soft tissues. The radio-

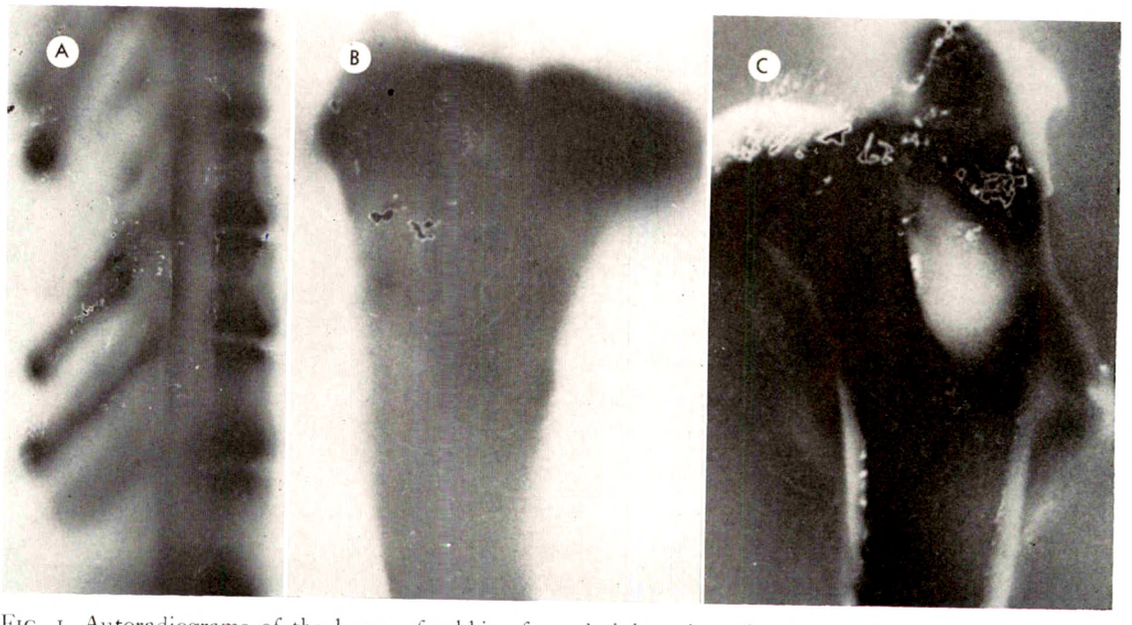


FIG. 1. Autoradiograms of the bones of rabbit after administration of radiophosphorus demonstrate the location of deposition of the radioisotope (from unpublished data, Tong, E.). (*A*) Dorsal spine. The vertebral bodies, spinous processes and the ribs show intense concentration of the radiophosphorus. The superior and inferior vertebral plates and the tip of the spinous process are particularly dense. (*B* and *C*) Humerus and femur. The spongiosa portion of long bones reveals more activity, particularly in the subchondral areas. There is lack of activity in the dense cortex.

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix Arizona, April 13–16, 1966.
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activity is predominantly localized in the spongiosa portion of bone; *i.e.*, the bodies of vertebrae, flat bones and metaphyseal ends of long bones[18] (Fig. 1, *A*, *B* and *C*). These are the areas where metastatic foci commonly occur.

3. *High differential uptake of radiophosphorus by malignant cells.* Clinical studies have shown that malignant cells take up relatively high concentration of radiophosphorus.[9] The same malignant tumor in a bone has a higher differential uptake of radiophosphorus than when it is located in soft tissue.[14] While malignant cells within bone absorb radiophosphorus constantly, malignant cells outside of bone absorb only that portion of radiophosphorus turned over from the bone after a state of equilibrium has been reached.

After administration of radiophosphorus, all gross and microscopic lesions in bone will be surrounded by and subjected to the strong beta irradiation emitted from radiophosphorus with a physical half life of 14.3 days and whose energy level is 1.7 mev. peak, and 0.69 mev. average. These beta particles, capable of penetrating to a maximum depth of 8 mm. (2 mm. average), produce intense localized ionization. While the radiophosphorus diminishes from the bone due to constant turnover, radioactivity in the tumor within the bone gradually increases because of the pick up and utilization by the rapidly multiplying malignant cells (Fig. 2).

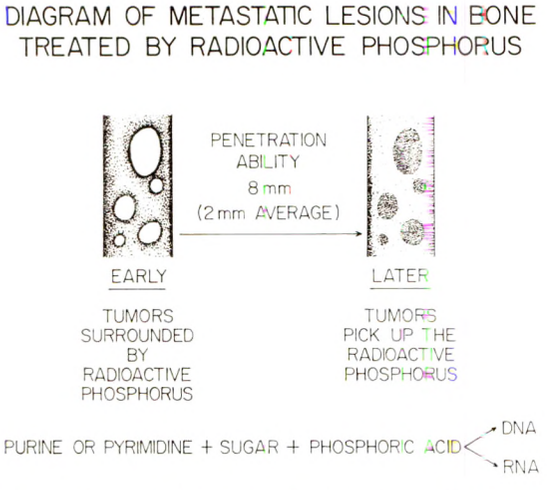


FIG. 2. Diagram shows the therapeutic mechanism of radiophosphorus when it deposits in bone. Initially, the tumor is irradiated by the beta particles which surround it. Later, while the isotope diminishes in the bone due to a constant turnover, the radiophosphorus concentrates in the rapidly multiplying malignant cells to be utilized for the formation of DNA and RNA. Transport of the isotope brings ionization within the tumor.

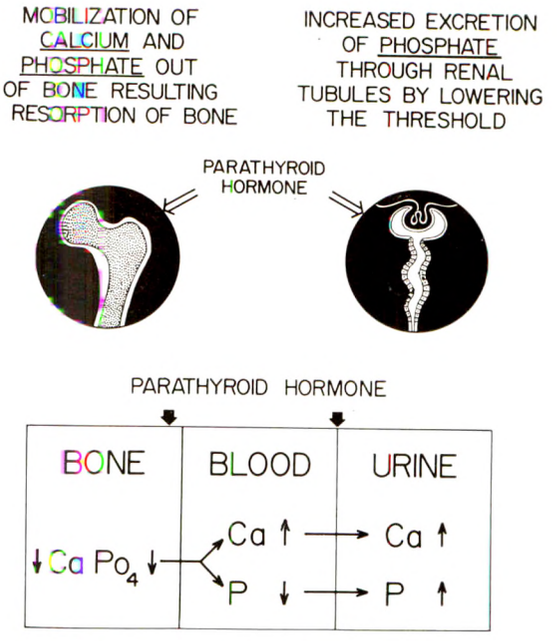


FIG. 3. Diagram illustrates the action of parathormone. By lowering renal tubular threshold, the urinary excretion of body phosphates is increased, resulting in hypophosphatemia. Simultaneously, it mobilizes the calcium and the phosphate out of bone producing hypercalcemia and hypercalciuria.

Parathormone was chosen to create, upon its withdrawal, a rebound effect which would lead to accelerated absorption of radiophosphorus in the bones and metastatic tumors. The rapid and enhanced deposition of radiophosphorus in bone was of dual advantage, not only in yielding intense focal ionization at the target organ, but also in decreasing circulating radioactivity, and consequently diminished total body irradiation. Albright, and Ingalls and co-workers[7] demonstrated the action of parathormone to be upon the renal tubules and bone. By lowering renal tubular threshold, urinary excretion of

body phosphates is increased, resulting in hypophosphatemia. Simultaneously, it mobilizes the calcium and phosphate out of bone, producing hypercalcemia and hypercalciuria (Fig. 3).

After administration of parathormone, a desaturation of minerals from the matrix of bone occurs, and upon removal of the hormone, the unsaturated bone will be avid for redeposition of calcium and phosphate. A rebound effect was observed shortly after discontinuance of parathormone. Along with marked reduction in the urinary output of calcium and phosphate, the blood calcium fell rapidly to normal or subnormal levels, while the diminished serum phosphorus reversed itself to a state of relative hyperphosphatemia. The diminished calcium in the blood returned to the bone as phosphate salts (Fig. 4).

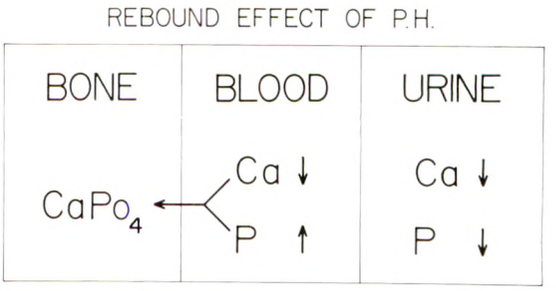


FIG. 4. Diagram illustrates the rebound effect of parathormone. A reversed effect is observed upon withdrawal of the hormone when the urine calcium, phosphorus and serum calcium diminish, and the serum phosphorus rises. The calcium is returned to the bone as the phosphate salt. P.H. = parathyroid hormone.

Therefore, radiophosphorus given after withdrawal of parathormone will be absorbed in the bone more rapidly and in higher concentration than what would oc-

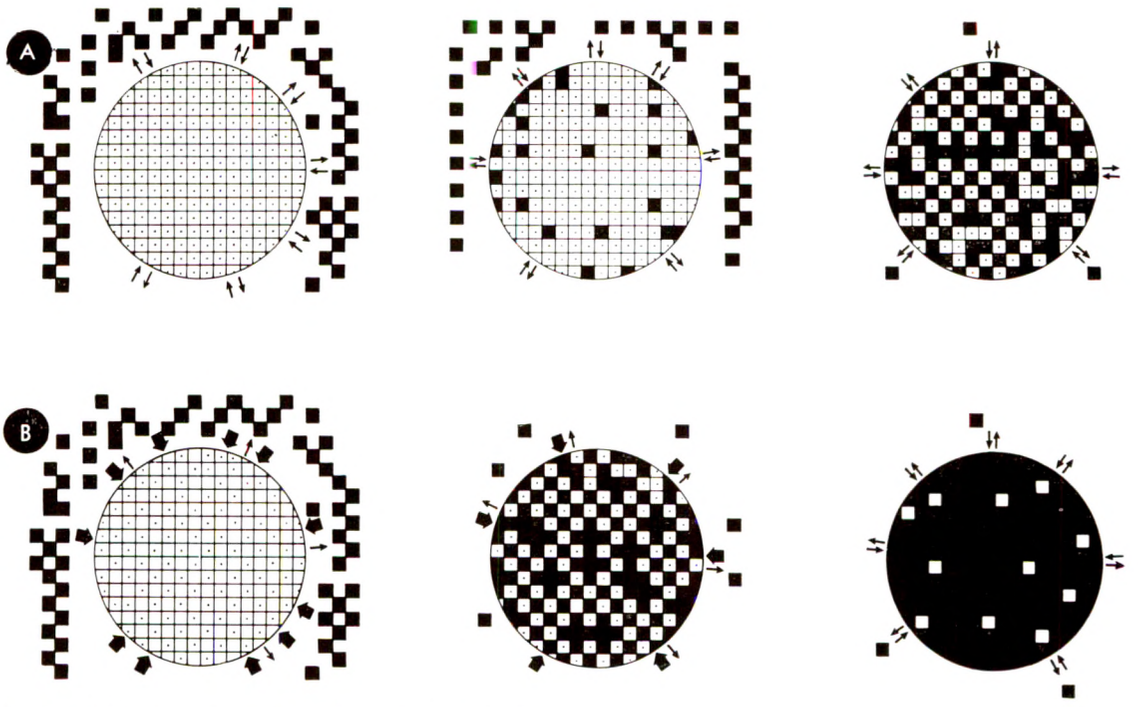


FIG. 5. Diagram showing the differences in intensity of deposition of a given dose of radiophosphorus in a controlled bone (*A*) compared with a parathormone treated bone in rebound phase (*B*). The dark squares represent radiophosphorus and the dots in the light squares represent minerals within the matrix of bone. (*A*) Normal turnover rate and deposition of radiophosphorus in a normal bone saturated with minerals in the matrix. (*B*) Enhanced uptake of radiophosphorus due to the unsaturation of calcium phosphate in bone plus a strong rebound force, created by parathormone. The rapid and enhanced deposition of radiophosphorus in bone is of dual advantage, not only in yielding an intense focal ionization at the target organ, but also in decreasing circulating radioactivity with consequent diminished total body irradiation.

TABLE I

MATERIAL FOR STUDY

Case	Age	Sex	Diagnosis	Previous Treatments	Bone Metastases	Duration of Known Metastases
1	49	F	Carcinoma of rt. breast	Rt. radical mastectomy 10 months ago followed by postoperative radiation therapy	Diffuse osteolytic lesions involving the skull, whole spine and pelvis; collapse of bodies of L-1, L-3, L-4	1 mo.
2	69	F	Carcinoma of rt. breast	Rt. radical mastectomy 8 years ago; stilbestrol	Diffuse osteoblastic and osteolytic lesions over the ribs, whole spine and pelvis	6 mo.
3	69	F	Carcinoma of lt. breast	X-ray, Co^{60} and radium therapy to left breast 2.5 years ago; Co^{60} therapy to both hips 2 months ago	Diffuse osteolytic lesions involving the whole spine and both femoral heads	2 mo.
4	64	F	Carcinoma of rt. breast	Rt. radical mastectomy 9 years ago; x-ray therapy to dorsal spine $\frac{1}{2}$ month ago	Erosion of pedicle, T-4; compressed fracture of body T-11; osteolytic lesions in pubic bones	1 yr.
5	70	F	Carcinoma of lt. breast	Lt. radical mastectomy 5 months ago; Co^{60} therapy to left clavicle 1 month ago; stilbestrol	Pathologic fracture of left clavicle; diffuse osteolytic lesions in ribs	1 mo.
6	58	F	Carcinoma of lt. breast	Lt. simple mastectomy 15 months ago; leukeran 4.32 mg.; oophorectomy	Diffuse osteolytic lesions involving the skull, whole spine, ribs, sternum, pubic bones and both femora	2 yr. and 4 mo.
7	54	M	Undifferentiated carcinoma of lt. lung	Lt. pneumonectomy 6 months ago	Osteolytic lesions involving the left rib cage and body of L-4	1 mo.
8	79	M	Squamous carcinoma of lt. lung	Co^{60} therapy to right shoulder and left femur 2 months ago; nitrogen mustard	Osteolytic lesions involving right occipital area, right humeral head, and left femur	2 mo.

cur from the normal turnover rate of phosphorus in bone, particularly in patients with a negative calcium metabolism (Fig. 5, *A* and *B*).

MATERIAL AND METHODS

Based on these concepts, 8 patients with extensive bone metastases were treated with parathormone followed by radiophosphorus. Six patients had carcinoma of the breast with widespread metastases to bone. Two patients had bronchogenic carcinoma with metastases to many bones, liver and other organs (Table 1). Each patient was fully studied before treatment, including a complete physical examination, pathologic confirmation, roentgenograms, hematologic studies, serum and urine calcium and phosphorus levels, and serum alkaline phosphatase.

Parathormone (parathyroid extract, dated, fresh preparations, Lilly) was given intramuscularly in doses of 100 units 3 times daily for 6 to 8 days. The total period of time for injection namely, 6 to 8 days, was chosen because parathyroid extract will not be effective if used continuously after a period of 1 to 2 weeks, probably due to development of an antihormone.

Blood and urine calcium and phosphorus and alkaline phosphatase were determined at daily and 2 day intervals. Patients were instructed to drink large amounts of water in order to eliminate excess calcium in the blood to avoid its precipitation in the kidney. Complications secondary to hypercalcemia, *i.e.*, vomiting, diarrhea, muscular atony, cardiac irregularities, oliguria and anuria did not occur in any instance.

Twenty-four hours after withdrawal of the parathormone, the time when the rebound effect usually began, the first dose of radiophosphorus, as the sodium phosphate, was given intravenously by drip in 100 cc. of normal saline. Three patients received a total dose of 10 mc in 2 consecutive days. Two patients, because of depressed bone marrow and cachexia, received a single dose of 5 mc. Two patients received 2 mc daily for 10 days. It was felt that an intense dose in a short period was better than small doses over a longer period, in order to take advantage of the rebound effect which was more prominent in the first 2 or 3 days after withdrawal of the hormone. The intravenous route was preferred to assure complete absorption necessary for dosage calculation. In oral administration, the absorption is often incomplete, since as much as 25 per cent of the administered dose may be excreted through the intestine.

Blood and urine samples were collected at daily and 2 day intervals for determination of radioactivity.

TABLE II

TIME OF APPEARANCE OF MAXIMUM EFFECTS AND THE REBOUND PHASE

Case	Dose of Parathormone	Maximum Effects of P.H.	Rebound Phase of P.H.	
			Onset	Duration
1	100 u BID for first 6 days; 50 u BID for next 6 days	on the 6th day	24 hr. after discontinuance of P.H.	6 days
2	100 u TID for 7 days	on the 6th day	24 hr. after discontinuance of P.H.	5 days
3	100 u TID for 8 days	irregular	24 hr. after discontinuance of P.H.	4 days
4	100 u TID for 7 days	on the 7th day	24 hr. after discontinuance of P.H.	7 days
5	100 u TID for 8 days	on the 7th day	24 hr. after discontinuance of P.H.	5 days
6	100 u TID for 7 days	on the 7th day	24 hr. after discontinuance of P.H.	2 days
7	100 u TID for 7 days	on the 7th day	24 hr. after discontinuance of P.H.	2 days
8	100 u TID for 3 days	on the 3rd day	24 hr. after discontinuance of P.H.	2 days

P.H. = parathyroid hormone.

TABLE III

CHANGES OF CALCIUM AND PHOSPHORUS IN SERUM AND URINE INDUCED BY PARATHORMONE INJECTIONS

Case	Serum Ca (mg. %)			Serum P (mg. %)			Urine Ca (mg./24 hr.)			Urine P (mg./24 hr.)		
	Before P.H.	Maximum during P.H.	Rebound P.H.	Before P.H.	Maximum during P.H.	Rebound P.H.	Before P.H.	Maximum during P.H.	Rebound P.H.	Before P.H.	Maximum during P.H.	Rebound P.H.
1	12.6	16.8	13.5	4.1	3.0	3.6	720	1,220	600	800	1,600	350
2	8.2	9.1	8.2	4.4	2.9	4.5	50	112	42	380	640	112
3	8.9	10.7	9.1	4.3	3.2	4.9	100	260	45	600	820	200
4	9.2	10.8	9.7	4.6	3.4	4.8	240	510	190	600	700	180
5	8.3	9.7	8.6	2.8	2.3	3.4	150	540	130	300	700	130
6	9.8	10.6	9.2	4.0	3.1	4.2	175	520	120	350	885	192
7	9.8	10.4	9.5	4.5	3.3	5.7	350	865	104	225	655	291
8	9.6	10.2	8.5	4.6	4.4	5.0	140	480	100	320	760	140

P.H. = parathyroid hormone.

Patients were given vitamin D, 4,000 units and calcium gluconate, 15 gm. daily in divided doses after the administration of radiophosphorus, to accelerate re-deposition of calcium phosphate in the unsaturated bone.

RESULTS

All patients manifested response to the parathormone by an increase in serum calcium and decrease in serum phosphorus. The changes varied considerably; for instance, Case 1 showed a rise of calcium from 12.6 mg. per cent to a maximum of 16.8 mg. per cent, whereas Case 2 showed an increase only from 8.2 mg. per cent to 9.1 mg .per cent. Similarly, decreases in serum phosphorus varied, as seen in Table III in Cases 2 and 8.

Simultaneous with the changes in the serum, there occurred a pronounced and more characteristic increase of calcium and phosphorus in the urine, often doubling in quantity within 24 hours. Cases 1, 2, 3, 4, and 7 showed doubling of calcium output in the urine under parathormone influence. In Cases 5, 6, and 8, the increase more than doubled, and even reached 3 times the original levels. Regarding phosphorus in the urine under hormone stimulation, the output doubled in Cases 1, 5, 6 and 8; trebled in Case 7; and in Cases 2, 3, and 4, the increase was about 20 per cent (Table III). Incidentally noted also was a copious outpouring of urine. These effects of parathormone injections were maximum on the 6th to 7th day.

Within 24 hours after withdrawal of the parathormone, there appeared a rapid reversal in the calcium and phosphorus in the serum and urine, along with diminution in urinary output, indicative of the rebound phase. Whereas the calcium and phosphorus returned to their former levels in the serum, they fell to levels lower than their originals in the urine. The rebound phase persisted for periods from 2–7 days, averaging 4 days (Table II). Figures 6 and 7 show the changes of calcium and phosphorus in serum and urine during and after administration of parathormone in Case 2.

After intravenous administration of the

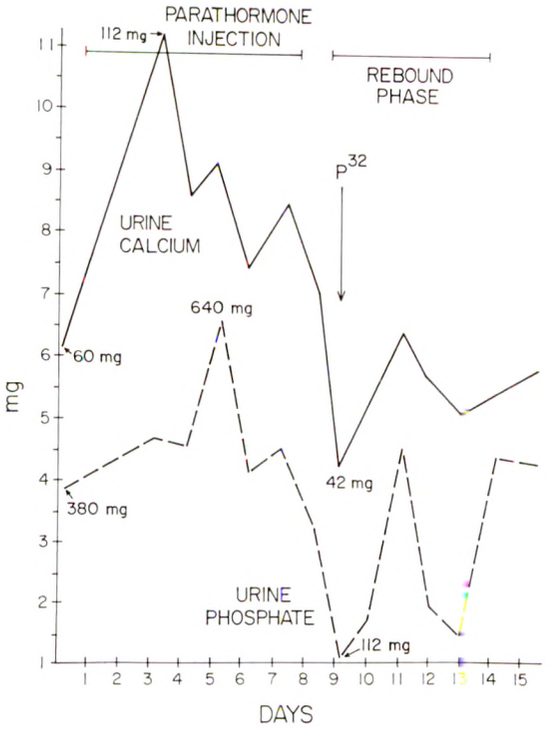


FIG. 6. Changes in calcium and phosphate in urine during and after injection of parathormone. During injection, the daily excretion of calcium rose from 60 mg. to the maximum of 112 mg.; the excretion of phosphate increased from 380 mg. to the maximum of 640 mg. Twenty-four hours after discontinuance of parathormone, there occurred a rapid fall in the daily excretion of calcium and phosphate to subnormal levels of 42 mg. and 112 mg., respectively. This reversal indicates the rebound phase when radiophosphorus is given.

radiophosphorus, all hematopoietic elements began to diminish. The leukocytes and platelets showed more significant depression compared with the hematocrit and hemoglobin. For instance, as shown in Table IV, in Cases 4 and 6, the white blood cells fell below the critical level of 3,000 cells per cubic mm., and in Cases 1, 3, 5, and 8, the leukocytes varied between 3,500 and 3,700 per cubic mm. Similarly, the platelets showed extreme sensitivity as seen in Cases 4, 5, 6, and 8, where counts near or below 50,000 were reached. One patient, Case 6, who had depressed bone marrow at the time when therapy was begun, developed aplastic anemia, requiring repeated blood transfusions. Recovery of all blood elements began after 6 weeks and return to normal was complete at the end of 2 to $2\frac{1}{2}$ months. The sequence of depression and recovery is well illustrated in Figure 8, derived from findings in Case 4.

The effective half life of radiophosphorus in the body, determined by measurements of radioactivity in whole blood, serum, and blood cells was found to be 8.5 days. Most of the activity disappeared from the serum within the first 24 hours (Tables V, VI, VII, and VIII; and Fig. 9).

Six of the 8 patients reported relief from pain. The degree of improvement varied from complete to moderate disappearance. In 3 patients, relief was dramatic, per

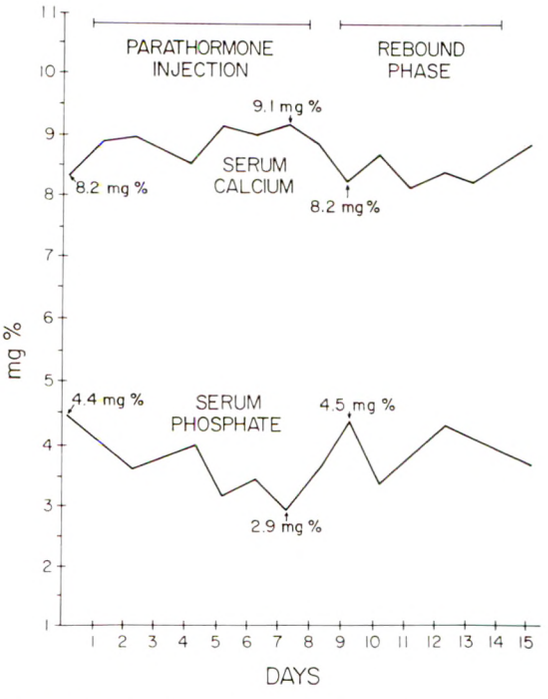


FIG. 7. Changes in calcium and phosphorus in serum during and after injection of parathormone. During injection, calcium rose from 8.2 mg. per cent to the maximum of 9.1 mg. per cent on the 6th day. At the same time, serum phosphorus fell from 4.4 mg. per cent to the minimum of 2.9 mg. per cent also on the 6th day. Twenty-four hours after discontinuance of the hormone, there was a reversal in the levels, indicative of rebound phase, when calcium fell to its original of 8.2 mg. per cent and the phosphorus returned to its previous 4.5 mg. per cent.

Table IV

CHANGES (IN BLOOD) AND RESULTS AFTER ADMINISTRATION OF RADIOPHOSPHORUS

Case	Dose of P^{32}	Hemoglobin gm. %		Hematocrit %		Leukocytes		Platelets		Clinical Results
		Before P^{32}	After P^{32}	Before P^{32}	After P^{32}	Before P^{32}	After P^{32}	Before P^{32}	After P^{32}	
1	5 mc×2	12.5	9.6	36.0	32.0	5,500	3,700	240,000	100,000	No relief of pain; died in 2 months
2	5 mc×1	12.0	9.0	35.0	29.5	10,000	7,500	360,000	160,000	Complete relief of pain; increase of strength; died in 2 months
3	5 mc×2	10.9	8.2	38.0	33.0	8,100	3,600	250,000	110,000	Moderate relief of pain; died in 2 months
4	2 mc×10	13.7	10.0	41.0	34.0	6,950	2,800	200,000	50,000	Complete relief of pain; re-calcification of osteolytic lesions; died in 5 months
5	5 mc×2	10.1	8.0	34.0	28.0	5,700	3,500	280,000	65,000	Complete relief of pain; died in 7 months
6	5 mc×1	8.4	5.5	22.5	16.5	4,800	1,000	82,000	46,000	No relief of pain; died in 5 months after repeated blood transfusions
7	2 mc×4	12.4	9.8	34.5	30.5	9,000	9,450	225,000	324,000	Moderate relief of pain; died in 2 weeks
8	2 mc×10	10.0	8.5	34.0	27.0	6,000	3,750	204,000	60,000	Moderate relief of pain; died in 1 month

mitting return to household duties. The satisfactory change was obvious to these patients, because they had been subjected to conventional methods, such as cobalt 60 therapy, and/or chemotherapy, and/or hormones, without beneficial effect. The patient with severe bone marrow depression requiring transfusions reported no relief from pain.

One patient, Case 4, showed re-calcification in many of the osteolytic metastases 1 month after therapy (Fig. 10, *A* and *B*; 11, *A* and *B*; and 12, *A* and *B*).

Case 7, died 2 weeks after administration of the radiophosphorus and autopsy was performed. Specimens from various organs were measured to determine radioactivity per gram of tissue. The tumor within the liver, the ribs, and vertebral bodies had greater activity in contrast to other soft tissue organs such as spleen, kidney and muscle (Table IX; and Fig. 13). The vertebral bodies from D-11 through L-4 were bisected with a saw and removed. These bones were radioautographed for 7 days in a refrigerator, using industrial film kept in

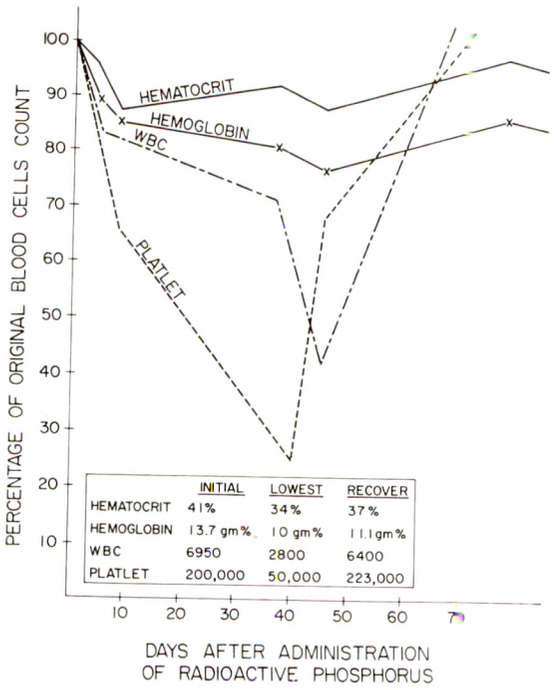


FIG. 8. The effect upon hemopoietic elements after administration of radiophosphorus. The platelets and leukocytes demonstrated greater sensitivity than erythrocytes. The recovery of all blood elements began at 6 weeks, then gradually returned to normal by the end of 9 weeks.

TABLE V

STUDY OF CLEARANCE OF RADIOPHOSPHORUS
URINE

Time after Administration of P^{32}	Volume/24 hr. (cc.)	Counts/min./cc.
1 da.	360	195,304
2 da.	450	76,271
4 da.	515	50,562
5 da.	510	46,875
6 da.	625	40,909
7 da.	875	19,562
8 da.	500	34,615
9 da.	650	18,518
10 da.	600	20,930
11 da.	825	13,235

TABLE VI

STUDY OF CLEARANCE OF RADIOPHOSPHORUS
WHOLE BLOOD

Time after Administration of P^{32}	Hematocrit (per cent)	Counts/min./cc.
5 min.	31	49,100
45 min.	31	24,861
4 hr., 20 min.		21,276
6 hr., 20 min.		20,689
17 hr.		23,809
4 da.		16,605
5 da.	34	16,363
6 da.	34	14,975
7 da.		12,950
8 da.	31	11,002
9 da.		11,842
10 da.	29.5	10,169
11 da.		9,259

TABLE VII

STUDY OF CLEARANCE OF RADIOPHOSPHORUS
SERUM

Time after Administration of P^{32}	Hematocrit (per cent)	Counts/min./cc.
5 min.	31	29,230
4 hr., 20 min.		13,392
5 da.	34	5,610
6 da.	34	5,565
7 da.		3,887
10 da.	29.5	3,722
11 da.		3,571

TABLE VIII

STUDY OF CLEARANCE OF RADIOPHOSPHORUS
BLOOD CELLS

Time after Administration of P^{32}	Hematocrit (per cent)	Counts/min./cc.
5 min.	31	19,868
4 hr., 20 min.		11,476
5 da.	34	12,875
7 da.		9,063
9 da.		8,264
10 da.	29.5	7,513

FIG. 11. (*A*) Lateral view of the dorsal spine shows the collapse of the body of T-11. There is destruction of the inferior margin of the body of T-10 with a widened intervertebral space between T-10 and T-11. (*B*) Re-examination after treatment shows increased density in the collapsed body of T-11. The intervertebral space between T-10 and T-11 returned to normal. There is reappearance of the inferior margin of the body of T-10.

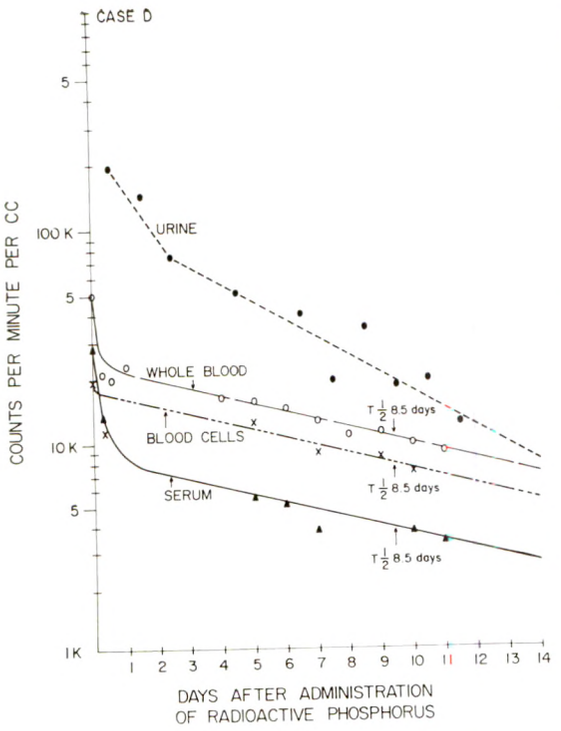


FIG. 9. Clearance of activity in the urine, whole blood, serum and blood cells after the administration of radiophosphorus. The effective half life of the radioisotope was 8.5 days. (Curves plotted from figures listed in Tables IV, V, VI and VII.)

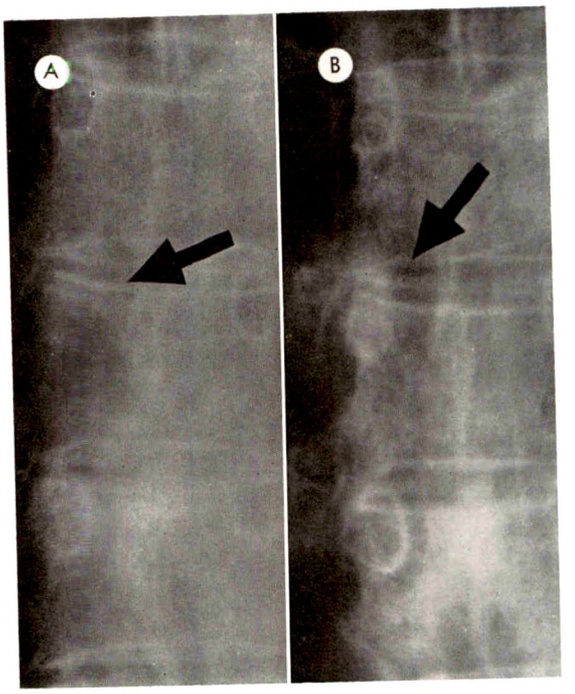
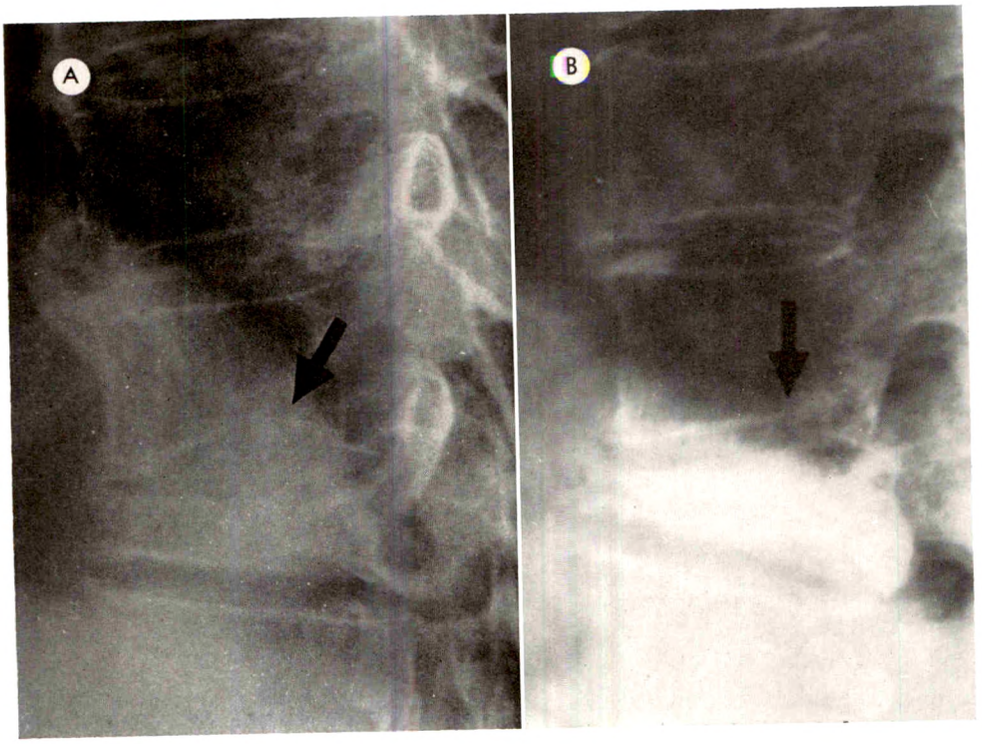


FIG. 10. Roentgenograms showing re-calcification of osteolytic lesions 1 month after administration of radiophosphorus. (*A*) Anteroposterior view of dorsal spine shows destruction of the right pedicle of T-4. There is also a radiolucency in the right lateral portion of the body of T-4. (*B*) Re-examination after treatment shows the reappearance of the right pedicle of T-4, and re-calcification of the osteolytic lesion in the body.



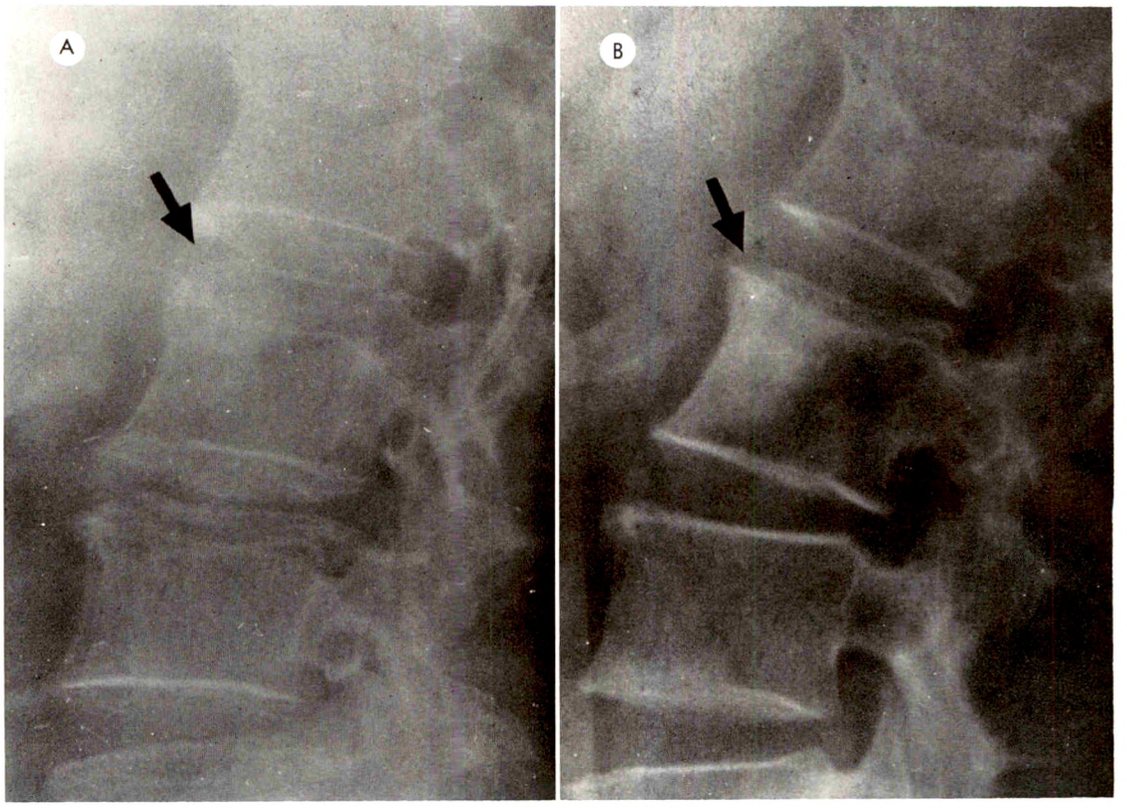


FIG. 12. (*A*) Lateral view of the lumbar spine showing the loss of clear demarcation of the superior border of the body of L-2. (*B*) Re-examination after treatment shows increased density in the anterior and superior portion of the body of L-2. The superior margin of this vertebral body is well demarcated at this time.

TABLE IX

UPTAKE OF RADIOPHOSPHORUS IN DIFFERENT TISSUES

Specimen (oven dried)	Dried Weight (gm.)	Counts (1,000 ×)/min.	Counts/gm. of (1,000 ×)/tissue
Tumor in liver	0.26	8.3	32.0
Tumor in thorax, adjacent to rib	0.55	10.1	18.5
Central portion of tumor in thorax	0.97	13.8	14.2
Rib	0.24	7.7	32.0
Vertebral body	0.86	23.0	26.8
Liver	0.82	12.5	15.3
Lung	0.7	11.8	17.0
Pancreas with tumor	0.88	12.3	14.0
Intestine	0.64	7.4	11.6
Spleen	1.17	13.4	11.5
Kidney	0.9	9.9	11.0
Heart muscle	0.75	6.5	8.7
Urinary bladder	1.21	9.0	7.4
Prostate	0.83	5.5	6.6
Straight muscle	0.72	4.6	6.4
Adrenal gland	1.03	4.1	4.0
Thyroid gland	0.82	3.0	3.7
Testis	0.88	3.3	3.7

Treatments: Parathormone 100 units TID for 7 days followed by P^{32} 2 mc daily × 4.

a light proof box. Figure 14, *A* and *B* vividly demonstrates deposition of radioactivity in the metastatic tumor as well as in the spongiosa.

DISCUSSION

Radiophosphorus with an energetic beta emission capable of destroying tumors locally, if it can be made to concentrate in the target area, constitutes an ideal radiopharmaceutical. This investigation was directed to the application of the physiologic actions of parathyroid hormone to achieve this objective. Sudden withdrawal of the hormone resulted in rapid re-deposition of calcium phosphate in the unsaturated bone. Radiophosphorus, given at this time, will be absorbed to the maximum.

The study will be pursued. An optimum time/dose will need to be established. Liver

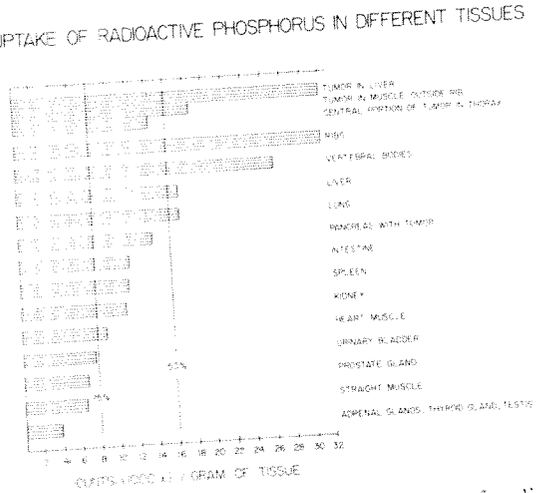


FIG. 13. Bar graft illustrating the uptake of radiophosphorus in specimens from different tissues obtained from autopsy of Case 7. The tumor within the liver, the ribs and vertebral bodies had a greater activity in contrast to other soft tissue organs.

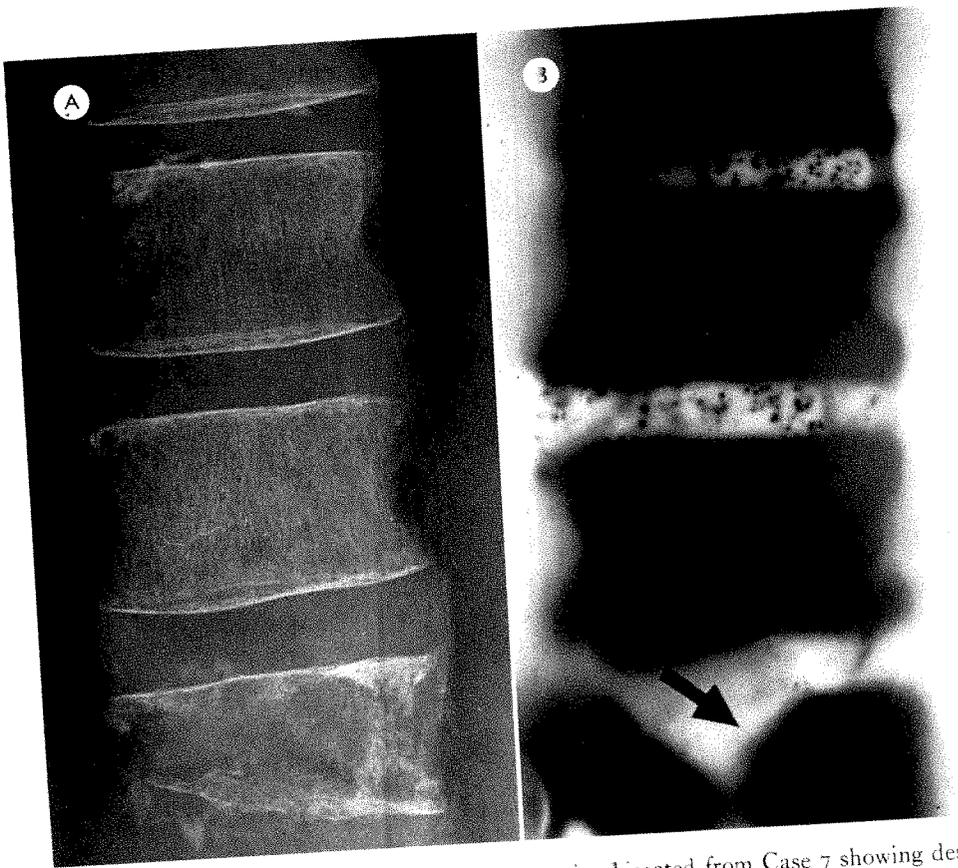


FIG. 14. (*A*) Roentgenogram of the specimen of lumbar spine bisected from Case 7 showing destruction of the body of L-4 by metastatic tumor. (*B*) Autoradiogram of the specimen shows the presence of radioactivity in the metastatic tumor as well as in the vertebral bodies.

TABLE I

CLASSIFICATION OF 62 CASES OF BONE SARCOMAS (1947–1963)

	Total	M	c	p	sy.	sy. M	M	i.c.	lf
Osteosarcoma	8	—	5+1*	2	4	—	+1*	—	1
Chondro-osteomyxosarcoma	16	1	14	2	4	—	6	—	4(2M)
Fibro-Spindle-Polymorphocellular Sarcoma	14	5	7+1*	6	3	2	1+1*	—	1(M)
Ewing and Reticulum Cell Sarcoma	14	2	9	5	2+1+	—	4	1	1(M)
Without Histology	52	8	35+2*	15	13+1+	2	11+2*	1	7
	10	1	7	3	4+1o		3		

*= Incomplete radiologic treatment and operation.
+ = Living (2 years) but no follow-up.
o = Living free of disease after palliative treatment.
M = distant metastases.
c = curative treatment.
p = palliative or interrupted treatment.
sy. = symptom free.
sy. M = histologically locally free of disease, distant metastases.
M = distant metastases, clinically no signs of tumor.
i.c. = intercurrent disease.
lf = local failure.

followed by amputation when the tumor could not be controlled locally, provided that in the interim no distant metastases had appeared. Reticulum cell and Ewing sarcomas received 4,000–5,000 r. Since 1953, curative treatment was carried out with 30 mev. roentgen rays, and since 1958 most often high speed electron beam therapy was used.

RESULTS

At present, our total results are still unsatisfactory. Thirteen out of 52 patients with histologically proven tumors are living without a trace of disease, more than 2 years following irradiation, or surgery and irradiation. In addition, one girl who had a reticulum cell sarcoma of the femur is living and able to walk, but has not returned for follow-up examination.

Osteosarcoma seems to be more responsive than tumors with cartilage formations. Figure 1*A* shows a partly removed osteogenic sarcoma of the right tibia in a 9 year old boy. He received 5,700 r in 25 days with 30 mev. roentgen rays. Figure 1*B* shows the patient 8 years later. He had been free of disease for more than 10 years.

Fibrosarcomas of the bone produce distant metastases in the initial stages much more often than other tumors. This is in



FIG. 1. Partially removed osteogenic sarcoma in a 9 year old boy. A dose of 5,700 r in 25 days with 30 mev. roentgen rays was administered. (*A*) Before roentgen therapy. (*B*) Eight years later.

contrast to fibrosarcomas of the soft tissue and represents a curious parallel to sarcomas of the thyroid gland, which are frequently seen in Switzerland; they also metastasize very early and cannot be cured. A case of polymorphocellular sarcoma of the right femur which was irradiated with 5,000 r in 42 days with 30 mev. roentgen rays is illustrated in Figure 2, *A* and *B*. Figure 2*B* shows the patient 9½ years later. Osteonecrotic bone is surrounded by new bone formation.

In reticulum cell and Ewing sarcomas, our results are not as good as those of Parker and Jackson.[4] Their results are unique in the literature. We have lost most of our cases becauses of metastases. Five of 10 patients, however, who have not had histologic examination are living and free of symptoms.

THE QUESTION OF BIOPSY

We have observed the criteria of clinical classification in all cases of sarcomas of the bone very carefully. We did not have any histologic confirmation because either the prognosis at the beginning, after reliable clinical findings, appeared to be extremely unfavorable or, in 4 cases, because a biopsy was probably performed too late following irradiation. The histologic study showed only connective tissue and no signs of an inflammatory process. Another example is the case of a girl with a tumor of the humerus. Figure 3*A* shows the characteristic pathologic arteriogram of osteogenic sarcoma. No biopsy was made since the roentgenogram of the lung also showed a coin lesion which was considered to be a metastatic focus. Conventional roentgen ray therapy was given, delivering a dose of 3,570 r in 14 days. Treatment was terminated early because the tumor was exceedingly radiosensitive. The patient received a podophyllin preparation for a period of 3 years. The lung focus disappeared. The patient is free of disease for more than 4 years following treatment (Fig. 3*B*). In this group of cases, it appears that biopsy without preoperative irradiation may favor the dissemination of disease. In one-fourth of our cases with previous biopsy or incomplete surgery, distant metastases appeared within 3 months. We feel, therefore, that radiation therapy prior to surgery is the best method of reducing the possibility of metastases, although statistically such proof is lacking.



Fig. 2. Polymorphonuclear cell sarcoma in a 16 year old boy. A dose of 5,000 r in 42 days with 30 mev. roentgen rays was delivered. (*A*) Before roentgen therapy. (*B*) Nine and one-half years later.

CLINICAL COURSE OF THE DISEASE

We have endeavored, by studying the subsequent clinical course of the disease, to establish the local effect of irradiation. Two patients with negative histologic findings locally died of metastases. Eleven patients without any local signs of recurrence died of distant metastases, and 2 died of metastases due to inadequate irradiation followed by surgical removal of the tumor. If we take the mean between the minimum of 7 and the maximum of 18 possible failures, we obtain a figure of 36 per cent of local

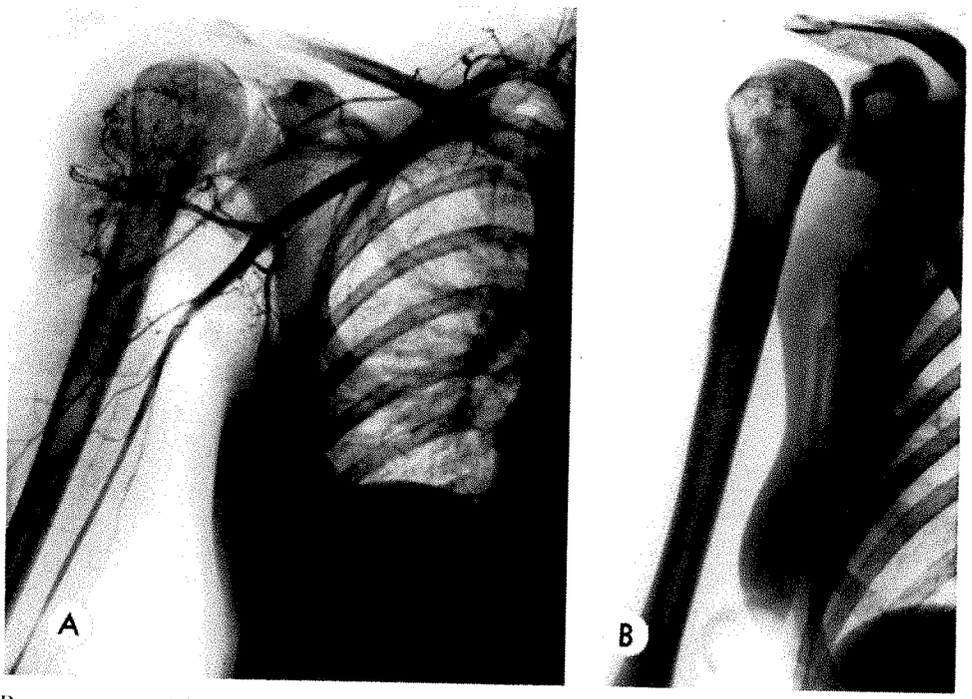


FIG. 3. Bone sarcoma with characteristic arteriogram and lung metastasis. No histologic study. Irradiation with a dose of 3,570 r of conventional roentgen rays in 14 days. (*A*) Before treatment. (*B*) Four years later. The lung metastasis also disappeared.

failures. A good periodical follow-up may detect some patients who develop a local recurrence and still have a good chance of cure by surgery. Table II gives the 3 year and 5 year results. The difference is small, only 1 patient dying of distant metastases between the 3 and 5 year period. The absolute 5 year result is more then 20 per cent and the relative result is approximately 30 per cent. Baclesse[3] observed 2 recurrences even after a 10 year period. It is thus obvious that the presently used methods are not ideal for estimation of the clinical course of the bone sarcomas and can be improved upon.

COMPLICATIONS

The above described results can only be achieved with a high local dose. With the exception of very sensitive tumors, one

TABLE II

THREE AND 5 YEAR RESULTS IN BONE SARCOMA CASES

	Total	c	p	sy.	sy. M	M	i.c.	lf
Three Year Results	39	30	9	10	2	12	—	6
Without Histology	5	4	1	2	—	3	—	—
Five Year Results	31	25	6	7	2	11	1	4
Without Histology	3	3	—	1	—	2	—	—

c = curative treatment.
p = palliative or interrupted treatment.
sy. = symptom free.
sy.M = histologically locally free of diseases, distant metastases.
M = distant metastases, clinically no signs of tumor.
i. c. = intercurrent diseases.
lf = local failure.

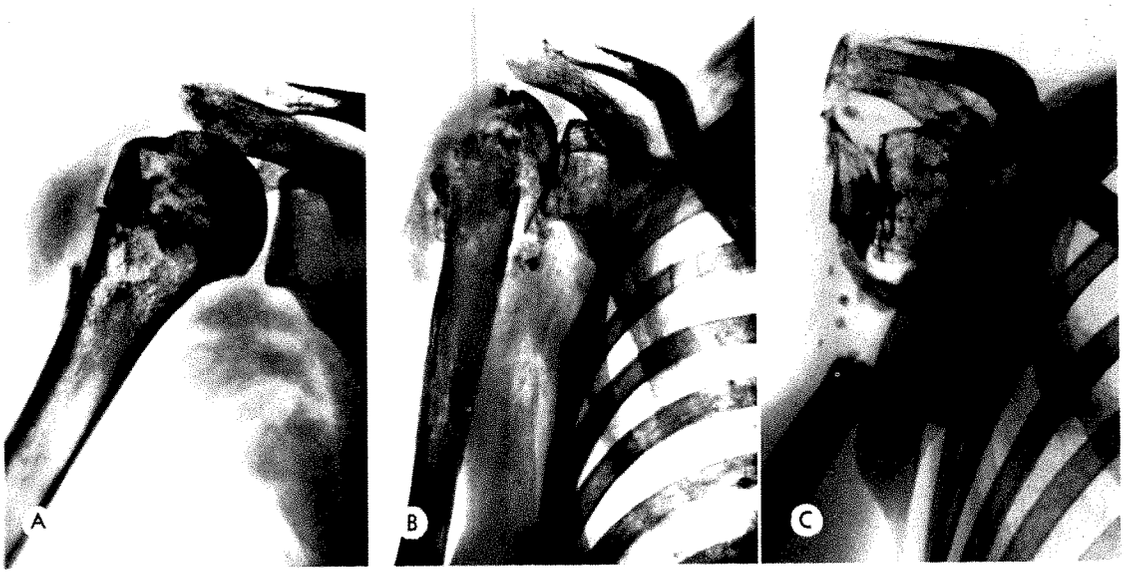


Fig. 4. Osteogenic sarcoma with incomplete surgery and pathologic fracture. Irradiation with 4,090 r in 30 days and 4,030 r in 21 days with 1 month interval. (*A*) Before radiation therapy. (*B*) One year after irradiation: bone necrosis. (*C*) Pseudoarthrosis 17 years later.

must run the risk of bone necrosis. Also, a large number of complications occurs. Three of our patients presented pathologic fractures which healed spontaneously. Five local ulcerations were seen which occurred at the site of a former biopsy or previous surgery; 4 cases had amputations and in 3 of these no sign of disease was found in the histologic preparations. One case had no histologic examination.

An example of bone necrosis is shown in Figure 4, *A*, *B* and *C*. This 16 year old female had incomplete surgery of an inoperable osteogenic sarcoma of the humerus with a pathologic fracture. Conventional roentgen therapy, using a dose of 4,090 r in 30 days in a first series and, after an interval of 1 month, a dose of 4,030 r in 21 days in a second series, was given. Radionecrosis of the bone developed which led, after unsuccessful surgery, to pseudoarthrosis. The patient is well 17 years after the treatment.

RECOMMENDED PLAN OF TREATMENT

A correlation of the results with the various forms of irradiation can not be established with any degree of accuracy, but high voltage radiation therapy seems to yield more favorable results.

We feel that the following procedures can be recommended:

1. Confirmation of diagnosis by clinical findings or plain roentgenography and, whenever possible, by arteriography. If the diagnosis is still uncertain, an excisional biopsy should be performed.

2. If the diagnosis is most probably a sarcoma of the bone, pre-irradiation according to the response of the tumor with doses of 2,000–4,000 r, biopsy, and then further radiation therapy, using doses of 6,000–8,000 r as soon as the wound has healed, should be given.

3. If a recurrence is suspected or the tumor persists, amputation should be performed if no distant metastases are present.

B. SARCOMAS OF THE SOFT TISSUE

This discussion will be confined to 3 types of tumors: (1) fibrosarcomas; (2) malignant synoviomas; and (3) lymphosarcomas.

FIBROSARCOMAS

The group of fibrosarcomas will be discussed first. The round cell sarcomas, which in our view display a strongly varying and unpredictable responsiveness to ionizing radiation will not be considered here. Fibrous

sarcomas, arising from the connective tissue, also vary very much. Fibrosarcomas and spindle cell sarcomas usually grow slowly, especially at the beginning, and may present several postoperative recurrences for years before forming distant metastases. They are known to be relatively resistant to ionizing radiation. The other sarcomas grow more rapidly, especially the polymorphocellular sarcomas. They show a better response, but have a poorer prognosis due to earlier and more frequent metastases. Ackerman and del Regato[2] state that among liposarcomas there are some which are radiosensitive.

On the whole, the results, up to the present time, have been rather disappointing. In these cases, surgery is used most frequently. Schinz and Damm,[6] and Du Mesnil de Rochemont,[5] as well as others recommend preoperative irradiation and feel that this is the best method of all. They report a 30 per cent possible cure rate after 3 to 5 years. Based on this experience, we have changed to high speed electron beam therapy of these tumors.

Our first case was that of a 25 year old man with a fibromyxosarcoma of the popliteal region. He had had 2 recurrences after surgery and roentgen irradiation (Fig. 5*A*). We tried a curative dose using electron beam therapy, since he refused amputation of the extremity which was advised. In 30 days a dose of 7,960 r with 22 mev. was delivered. After a moderately severe exudative reaction, the fairly extensive infiltration in the fossa poplitea disappeared. The patient is still free of symptoms (Fig. 5*B*).

In all, 22 cases have been observed for more than 3 years. Six cases received only palliative treatment since distant metastases were present or because the primary tumor was too extensive and the general health poor. Twelve cases are well and 2 have died, free of local symptoms and



FIG. 5. Recurrent fibromyxosarcoma following surgery and roentgen irradiation with 190 kv. in a 25 year old man. Irradiation with 7,960 r in 30 days, using 22 mev. electron beam therapy. (*A*) Fossa poplitea before last treatment. (*B*) Six years later.

without metastases. A case of osteomyxochondrosarcoma is shown in Figure 6, presenting roentgenographically calcification in the soft tissue. Following excision of the sarcoma, a dose of 5,880 r in 29 days with 30 mev. electron beam therapy was delivered. The patient has been without symptoms for 7 years and has no complaints and no induration. The skin appears normal.

Similar to the conversion of an inoperable tumor into an operable one by preliminary irradiation, an attempt should also be made by using chemotherapy to convert tumors to a stage where irradiation is possible. In this respect, I would like to introduce a new term: *irradiable*. We must convert a non-irradiable tumor into an irradiable one. The future will then determine whether it will be possible to influence in this manner a further number of cases which had been incurable as a result of extension by rendering them curable.



FIG. 6. Thigh of a 12 year old girl with osteomyxochondrosarcoma with typical calcification in the soft tissues. Excision and irradiation with 5,880 r in 29 days using 30 mev. electron beam therapy. Free of disease 7 years later.

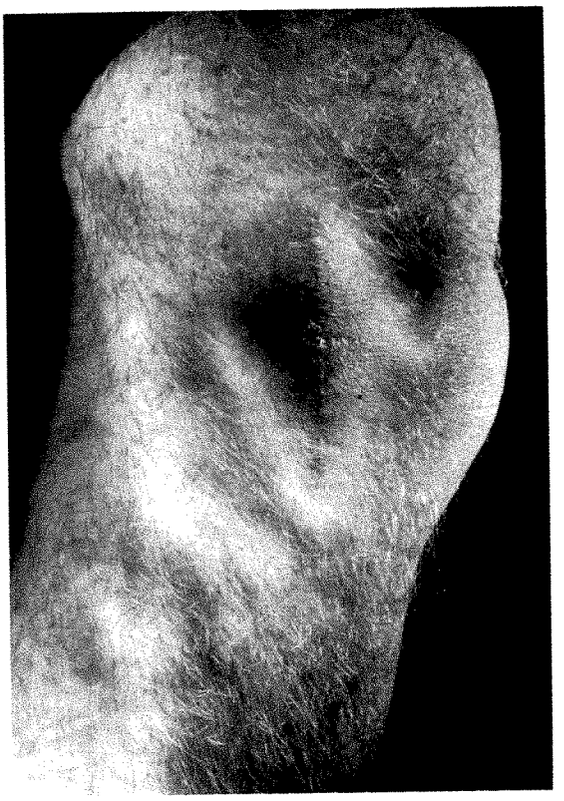


FIG. 7. Recurrent malignant synovioma in a 24 year old man. Irradiation with 6,000 r in 24 days, using 15 mev. electron beam therapy. Excision of the scar 2 months later. Microscopic examination negative. Free of disease 5 years later.

MALIGNANT SYNOVIOMAS

A special group of rare sarcomas are the highly malignant synoviomas. Occasionally, patients afflicted with this tumor live for some years, but the great majority die of their disease. We have seen 6 patients; 1 has not responded to high voltage roentgen therapy, and 5 showed a surprising response to electron beam therapy. Of these latter, 1 died of distant metastases but remained free of disease locally; the remaining 4 are alive and are free of symptoms (1 is alive only a short period after irradiation,



FIG. 8. Lymphosarcoma of the stomach with incomplete surgical removal. Irradiation with 6,100 r in 36 days, using 30 mev. roentgen rays. (*A*) Before irradiation. (*B*) Six years later. Free of disease 11 years after treatment.

followed by amputation, and the other 3 are living, free of disease, 4 and 5 years following conservative surgery and irradiation). Figure 7 shows the region of the knee of a 24 year old man with a recurrence, the size of a silver dollar, after conservative surgery and electron beam irradiation with 6,000 r in 24 days. Two months later the irradiated area was excised. No tumor was found histologically and primary healing of the wound ensued. The patient is free of disease 5 years later and is skiing regularly. The best method of treatment for these lesions seems to be total excision followed by electron beam therapy or, in the case of an inoperable tumor, radiation therapy followed by surgery.

LYMPHOSARCOMAS

The last group of tumors to be discussed includes a case of lymphosarcoma of the stomach.[11] This lesion, in many instances, is curable by high voltage roentgen ray therapy. Figure 8, *A* and *B*, shows a patient who was treated with this modality of irradiation after incomplete surgery 11 years ago. The tumor disappeared after 6,100 r in 36 days with 30 mev. roentgen rays. She is still in good health and shows no signs of disease.

Eleven other cases have been treated, but only 7 received curative irradiation. Six patients lived from 3 to 11 years free of symptoms; 2 died of metastases but were free of local symptoms. The doses varied between 5,000 and 6,900 r.

The author feels that if every case of sarcoma of the stomach were treated immediately with high voltage irradiation, either with the cobalt 60 or the betatron units, or with the linear accelerator, without waiting for a recurrence after surgery, a fairly high percentage of freedom from symptoms could be achieved.

SUMMARY

The opinion is expressed that, with the application of modern methods of radiation

therapy, a fairly high percentage of patients with sarcomas of the bone and soft tissue has a good chance of being cured.

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SINGLE DIAPHRAGM, FLEXIBLE, MULTIPLE PORT SYSTEM IN BETATRON THERAPY*

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THE original 22 mev. fixed horizontal beam betatron unit installed at the University of Illinois Medical Center in 1948 was subsequently provided with a number of limited field size collimating systems of heavy lead inserts weighing between 60 to 80 pounds each. The inserts had to be lifted into place for the daily treatments. Despite careful handling, these cumbersome inserts were subject to wearing, which necessitated frequent checking and the gradual discarding or restoring of some of them.

Due to the fixed horizontal direction of the beam, the patient had to be raised and adjusted carefully to the available ports.

Recently, as a result of a heavy load of patients due to increased interest in supervoltage therapy, we decided to introduce two new collimating systems, which were lighter, more flexible and would fit snugly within each other in a telescoping fashion. The patient sits comfortably on the treatment chair while the treatment ports are adjusted; thus, the treatment ports are easily reproduced.

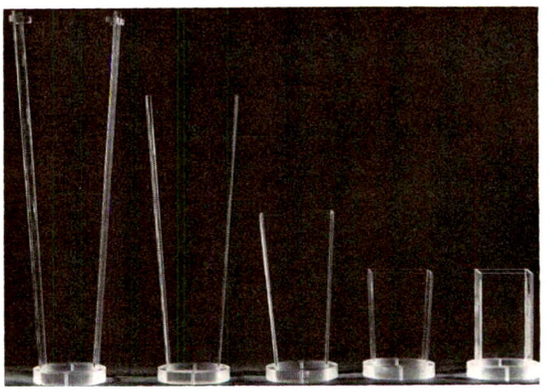


FIG. 2. Lucite cones of different sizes ranging from 13×20 cm. to 8×10 cm. in field size.

The original circular lead insert with a 10.5 cm. diameter opening, left permanently in the direction of the incident beam, provides a field size of 15 cm. in diameter at 80 cm. source skin distance. The output of

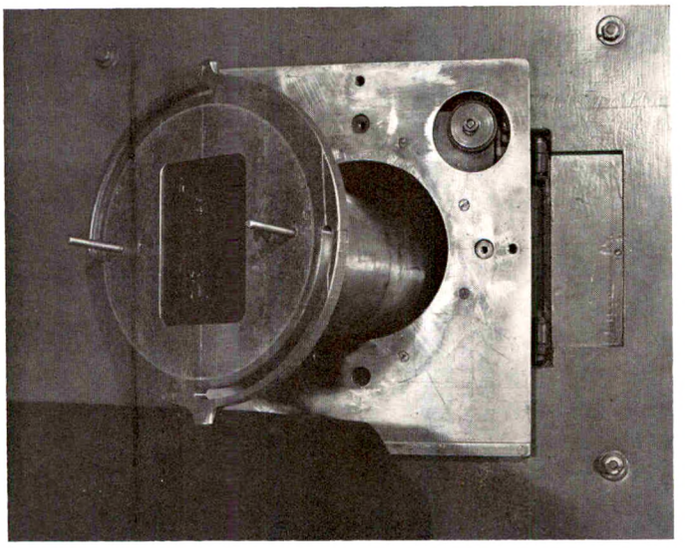


FIG. 1. New collimating system being inserted into the original circular lead insert. Only the front part is rotatable 360°.

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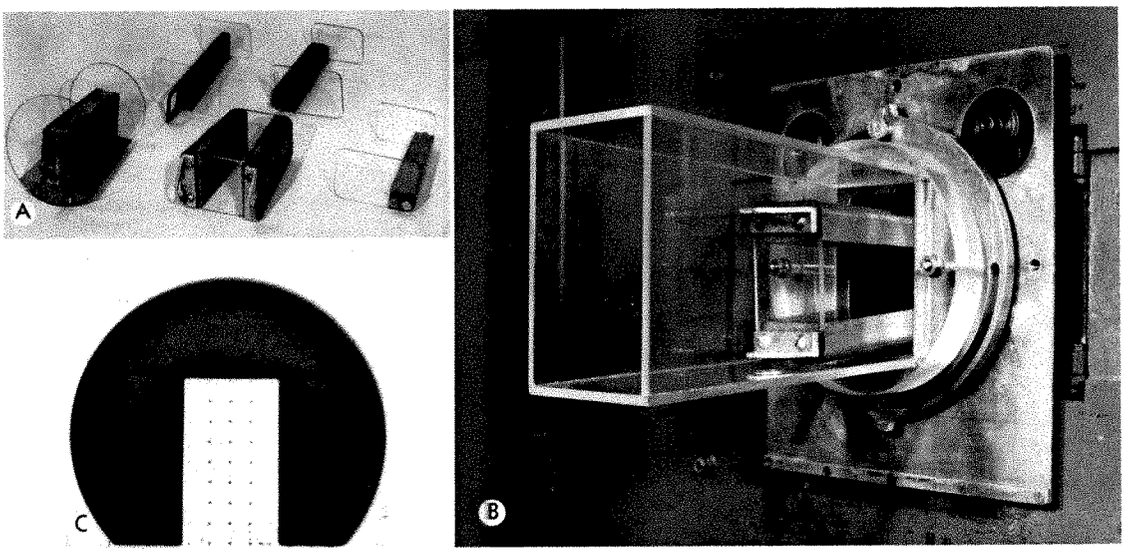


Fig. 3. (*A*) Tertiary lead inserts of different size for shaping the field of radiation desired. (*B*) Tertiary insert telescoped into the collimating system. (*C*) Photograph of a 15 cm. diameter pelvic port taken after blocking the central beam with a tertiary insert.

the betatron at this distance is 125 rads per minute.

A second conical insert weighing about 10 pounds provides an opening of 6×8 cm., and fits tightly into the original cone. Its outer surface is covered with a thin foil of brass, 0.1 mm. thick, to harden its surface while rotating against the circular cone. This cone has a flexibility of 360° rotation (Fig. 1).

From there on, multiple field sizes can be produced by adjusting lucite cones at different distances. These are lightweight and easily interchangeable (Fig. 2).

Tertiary small lead block cut-offs have been made to shape or reduce the field size in order to spare important structures; *e.g.*, the larynx while treating the supraclavicular regions, or points A and vagina in patients with carcinoma of the cervix treated initially with radium (Fig. 3, *A*, *B* and *C*).

These multiple insert devices have maintained a precise beam control and have proven to be highly satisfactory.

SUMMARY

A single diaphragm, flexible, multiple port system to be used in betatron therapy is described. Its advantages in the department and from the patient standpoint are discussed.

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THE SYNERGISTIC EFFECT OF LASER RADIATION AND IONIZING RADIATION ON MALIGNANT TUMORS *IN VIVO* AND *IN VITRO**

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THE laser can still be considered a new experimental device, even though considerable progress has been made in recent years in its application to biology and medicine. As an example, it has already been applied to melanoma patients,[1,4,8] as well as a series of nonpigmented tumors,[2] with encouraging results. These preliminary studies suggested that pigmented tissue is most responsive to the ruby laser, however. The vast majority of nonpigmented neoplasms require either large energy densities derived from massive instrumentation or lower laser energy levels used in combination with another therapeutic device.

The biologic effect of x-ray can be potentiated with either prior or subsequent exposure of the target material to far red or infrared ordinary light. Although many ingenious experiments have been performed, the mechanism of this potentiation has not yet been completely resolved. It has been considered that the far red light brought about either an increase in the x-ray-induced chromosome breakage,[6,10] or it decreased the restitution of the primary x-ray breaks.[3,5,9] In either event, this observation has not been applied, perhaps because conventional far red sources required treatment times which were inconvenient to both the patient and the radiologist.

The ruby laser was investigated as another intense far red light source using an established line of human adenocarcinoma (CMP) cells in tissue culture as a test object. The cells were routinely maintained in flasks or Rose multipurpose chambers, utilizing Eagle's medium supplemented with 10 per cent fetal calf serum.

The cell population was trypsinized with 0.25 per cent trypsin (Nutritional Biochemics Corp. 1–300) at pH 7.8 for 30 minutes at 37°C. The resulting suspension was counted with a hemocytometer and divided into 4 aliquots. The first set composed a group of unirradiated controls. The second was placed in a cylindrical cuvette, designed for measurement of optical rotation of polarized light. The internal diameter of the cuvette (7 mm.) matched the diameter of an unfocused beam emitted from a nominal ruby laser head (model 200, Hughes Aircraft Co.). After suitable alignment, the beam of laser energy was transmitted along the length of the cuvette, radiating the entire population of suspended cells. A series of 10 such exposures of 2 joules each was used for the laser treatment just prior to seeding and incubating in T30 flasks. The third set of cells was suspended in T30 flasks and exposed to a dose of 200 r gamma radiation from a Picker cobalt 60 teletherapy unit. The fourth set received the laser treatment and was then suspended in flasks for gamma radiation. Following a subsequent 4 day incubation period, the cells were again trypsinized, suspended in saline, and counted with a Coulter electronic cell counter.

Cell survival measured 4 days after irradiation was compared with the unirradiated cell population. Laser irradiation alone reduced the population to 87.7 per cent of controls. Exposure to 200 r gamma

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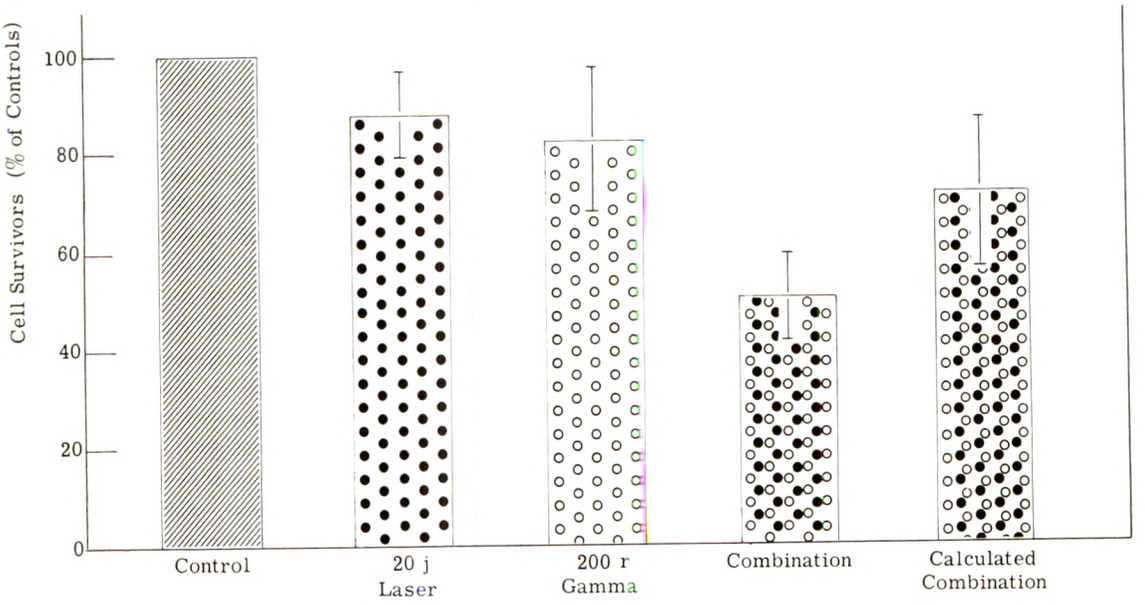


Fig. 1. The survival of irradiated populations of the CMP cell line relative to unirradiated controls. The bars represent average values obtained from replicate experiments. The vertical lines represent the range of standard deviations from the mean.

radiation depressed the cell number to 82.4 per cent of control values. A theoretic additive effect can be calculated if one considers that the combined factors would depress the control value by a per cent of a per cent. The calculated combination would be 87.7 per cent × 82.4 per cent or 72.3 per cent of controls. The observed combined effect was that the irradiated cell populations consisted of 49.7 per cent of the controls. These data, shown in Figure 1, indicate that laser radiation acted synergistically in combination with gamma radiation to depress the cell population.

McGuff *et al.*,[8] using human adenocarcinoma transplanted into hamster cheek pouches, reported similar findings. They observed histologically that all tumor cells were destroyed with 214 joules of ruby laser energy by the 5th post-treatment week. Irradiation of similar tumors with 1,000 r did not destroy the cells within the 6 week experimental period; instead, the tumor volume increased by 40.9 per cent. The combination of laser and roentgen rays produced death of all tumor cells within the 1st week of the post-treatment period.

With this experimental evidence in hand, the combined x-ray and laser therapy was considered for use on a patient with extensive reticulum cell sarcoma of the skin. This patient had numerous nodules, each measuring about 1.5 to 2 cm. in greatest diameter and elevated 3 to 5 mm. above the surrounding tissue, which were markedly reddish-purple in color and extremely tender. A biopsy confirmed the reticulum cell sarcoma diagnosis, and it was learned that approximately 1,200 r of radiation energy seemed to control these lesions using the 250 kv. machine with a half-value layer of 1.6 mm. of copper. Approximately 1 week following the last treatment, the lesions became asymptomatic and, except for a faint scar, appeared completely controlled. The patient was also screened with various chemotherapeutic agents with little effect except for some response to 5-fluorouracil. The patient's white blood cell count, however, had begun to show the effects of his extensive radiation therapy, as well as therapy with chemotherapeutic agents. Therefore, we elected to find some other form of therapy which might be successful. Since he had no visceral disease

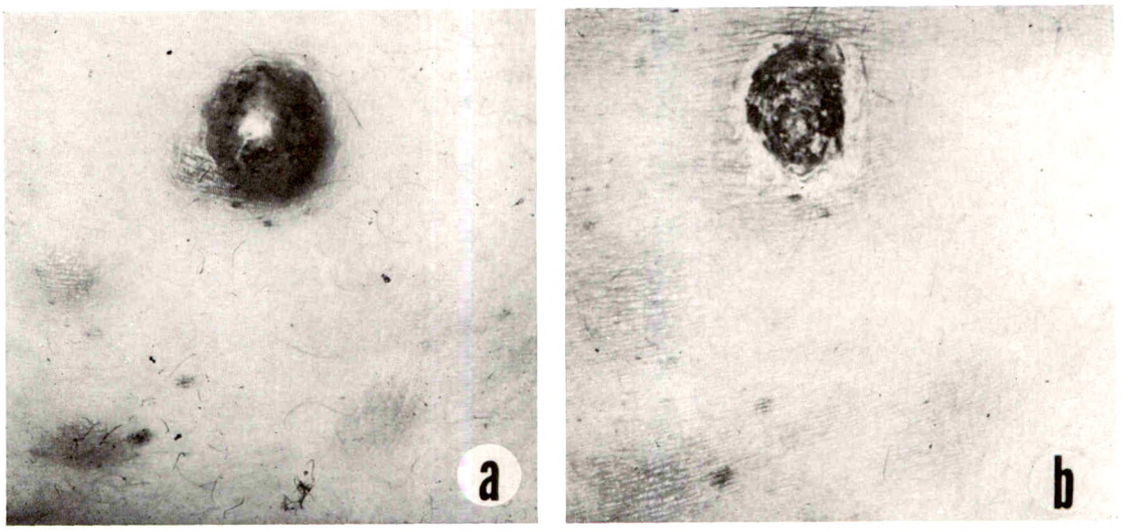


FIG. 2. (*a*) A reticulum cell sarcoma lesion prior to treatment with 10 exposures to a nonfocused 1 joule ruby laser beam. (*b*) The same area as in *a*, 19 days post-laser treatment.

discernible, we felt that the possible use of laser energy, either by itself or in combination with radiation energy, might provide for additional response. We carefully explained to the patient the implications of using this form of energy, and a cautious course of ruby laser therapy was initiated. It was found that approximately 10 firings of 1 joule each would cause the lesions to disappear in approximately 3 weeks (Fig. 2, *a* and *b*), whereas their shortest normal life history was about 10 weeks, and most persisted for an indefinite period. We then tried treating them with 300 r x-ray combined with 10 firings from the ruby laser. Using this therapy, the lesions were observed to disappear in about 1 week (Fig. 3, *a* and *b*). The patient became completely symptom-free after 3 months of this therapy, and remained so for approximately 6 months.

CONCLUSIONS

The nature of this preliminary study did not permit quantitation of the combined x-ray and laser therapy *in vivo*. However, the response of the lesions was consistent with the observed synergism in the *in vitro* study report of McGuff *et al.*[8]

The data from this study also appear to confirm previous reports that laser energy alone has some tumoricidal effect. However, we have recently observed that even a 100 joule focused ruby laser beam will not destroy muscle or kidney tissue beyond a depth of a few millimeters. This severe limitation is the result of several physical conditions, including the fact that scattering within the tissue prevents the accumulation of the required photon density for cellular disruption. It was further observed that a portion of the photons from a 20 joule unfocused ruby laser beam could be detected at a tissue depth of 5 cm., which can be considered important in the potentiation of x-rays at these depths.

Luckiesh[7] has indicated that the range of wavelengths which show optimal penetration of human tissue is from 10,000 to 12,000 Å. This suggests that a neodymium pulsed laser (10,600 Å) or a modified He-Ne continuous wave laser (11,500 Å) may have more value than the ruby laser for this purpose. Moreover, Swanson and Hollaender[10] reported that x-ray induced aberrations in *Tradescantia* microspores could be increased with wavelengths as long as 11,500 Å. The comparative value of infrared laser sources for the potentiation of x-ray is currently being investigated.

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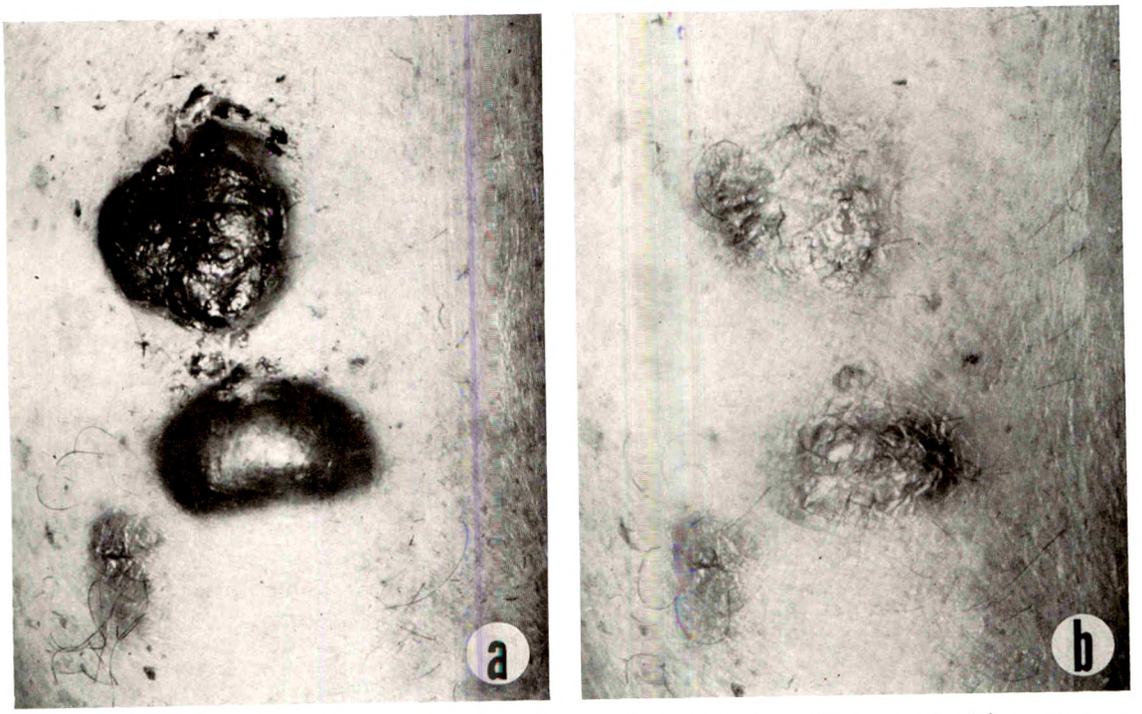


FIG. 3. (*a*) Two reticulum cell sarcoma lesions photographed at the time of treatment with 300 r x-ray followed with 10 exposures to a nonfocused, 1 joule ruby laser beam. (*b*) The same lesions, 5 days post treatment.

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ACCURACY IN MEASURING NODULES BY SCANNING*

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EXCELLENT scans can be obtained from phantoms which contain "hot" and "cold" nodules, but phantoms do not adequately represent the *in vivo* situation because: (1) the distribution of activity *in vivo* is not as uniform as that in a phantom; (2) background activity is absent in a phantom; (3) the gland *in vivo* is not parallel to the detector at all times as in the phantom; (4) the physical setting of the detector at the exact focal distance can easily be set on a phantom, but not on a patient; (5) the setting over the "hot" spot is simple and extremely accurate on a phantom, but not on a patient; and (6) movement with breathing, swallowing and coughing, etc., can cause smearing out of a defect in a scan on a patient, while there is no movement in a phantom.

This study was undertaken to evaluate the reliability and efficiency of an organ scan carried out *in vivo*. The accuracy of detection of a nodule within the organ was evaluated by comparison of scan lesion size to the dimensions of the lesion measured after its resection.

MATERIALS AND METHODS

Standard commercially available equipment was used to obtain the organ scans. The Nuclear Chicago, Picker and Baird Atomic units were evaluated and found essentially equivalent.

The detectors contained a 3×2 inch NaI (Tl) scintillation crystal detector and spectrometer electronics.

Thyroid scans *in vivo* were obtained 24 hours after oral administration of I^{131} sodium iodide. Kidney scans were performed a minimum of 1 hour after intravenous injection of Hg^{203} chlormerodrin.

The physical factors used in routine scanning are shown in Table 1.

RESULTS AND CONCLUSIONS

Scans were obtained pre- and postoperatively and on the same surgical specimen scanned *in vitro*. Not all surgical specimens were satisfactory for scanning, mainly because of insufficient radioactivity remaining in the specimen due to the time delay. Figures 1, *a-f*; and 2, *a*, *b* and *c* show the results of such comparative scans placed alongside photographs of the gross specimens. The scales have been adjusted for the enlargement factor for each scan or photograph, as indicated. With these scans of both thyroid and kidney, there is remarkable uniformity of the lesion size by *in vitro* scanning, and the gross lesion size measured directly.

In general, surgical specimens sent to the

TABLE I

PHYSICAL FACTORS IN ROUTINE SCANNING

Organ	Isotope	Dosage	Lower Level (Kev.)	Upper Level (Kev.)	Collimator (no. holes)
Thyroid	I^{131} Sodium Iodide	50 μc	324	404	61
Kidney	Hg^{203} Chlormerodrin	100 μc	229	329	37

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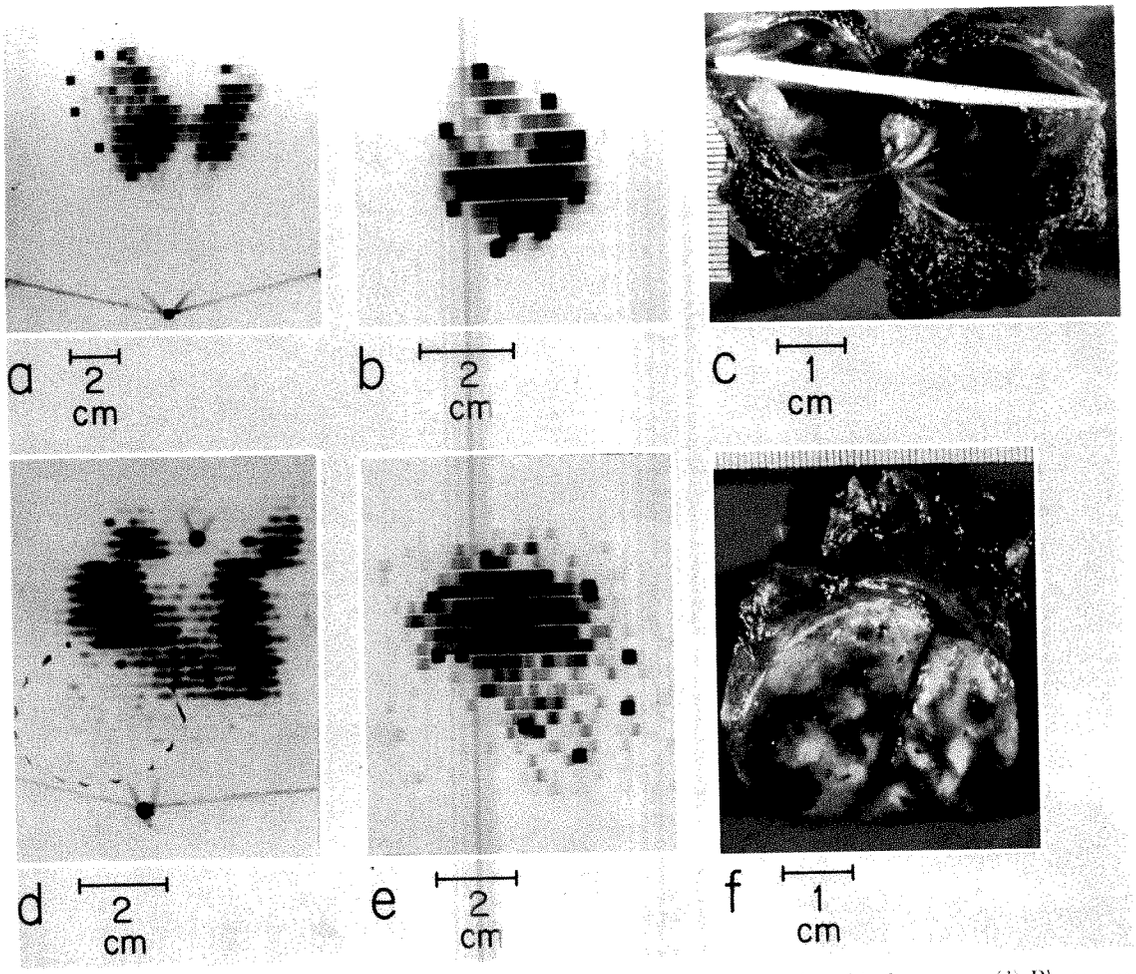


FIG. 1. Case 1. Pathologic diagnosis: adenomatoid goiter. (*a*) Preoperative thyroid photoscan. (*b*) Photoscan of right lobe after resection. (*c*) Gross photograph of pathologic specimen showing a large cyst.

Case 2. Pathologic diagnosis: follicular adenoma. (*d*) Preoperative thyroid photoscan. (*e*) Photoscan of right lobe after resection. (*f*) Gross photograph of resected specimen showing an encapsulated and focally necrotic tumor.

pathology department were processed in the routine manner. Measurements of nodules, encapsulated tumors and cysts were made. The dimensions of these lesions were recorded independently of the isotope laboratory measurements obtained from the scans, thus constituting a double blind series. In Table II, the thyroid scan lesion dimensions and the measured lesion size are given. The scan values are, of course, only in two dimensions, whereas the direct measurements were usually in three. The percent difference is computed from comparison of projected areas based on both sets of measurements. The sign of this value compares the scan dimensions with the dimensions of the actual specimen. There was an obvious tendency towards "rounding off," particularly of the values from the pathology department. This contributed somewhat to the variability of the two sets of numbers. The mean per cent difference was 20.6 ± 16.1. There is an over-all tendency for the scan values to be greater than the measured ones, but this is not consistent and would not be helpful in evaluating any given scan lesion size.

Similar evaluations with a variety of phantoms show negligible deviation of scan defect or "hot spot" size from the

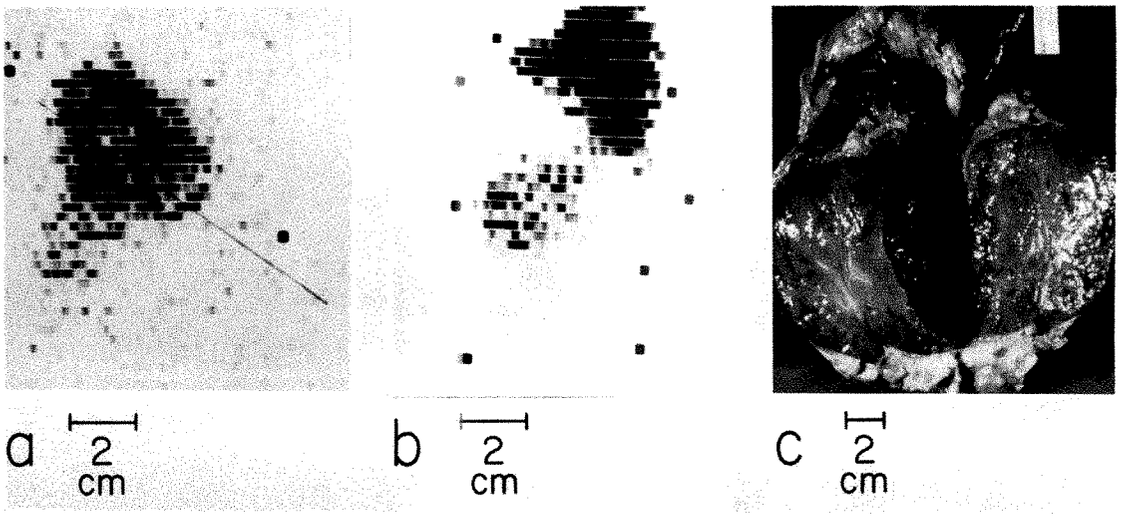


FIG. 2. Pathologic diagnosis: carcinoma of right kidney. (*a*) Preoperative renal photoscan. (*b*) Photoscan of right kidney after resection. (*c*) Gross photograph of bulky, encapsulated tumor that replaced the entire lower pole.

TABLE II

SCAN DIMENSIONS AND LESION SIZE

No.	Diagnosis	Scan Dimension	Pathology Dimensions	Per Cent Difference (Area)
		(mm.)	(mm.)	
1	Nodular goiter	55×40	45×35×20	+39
2	Thyroiditis, nonspecific	60×25	65×35	− 7
3	Hürthle cell adenoma	43×38	47×35	− 1
4	Follicular carcinoma	25×20	30×15×2	+11
5	Nodular thyroid	90×54	90×40×40	+13
6	Hashimoto's struma	20×11	25×10×5	−12
7	Follicular adenoma	92×48	85×50×20	+ 4
8	Follicular adenoma	68×30	60×25×25	+36
9	Epithelial lined cyst	44×20	40×16×8	+37
10	Papillary adenoma	21×16	25×25×25	−46
11	Thyroiditis, nonspecific	24×10	20×15×10	−20
12	Hashimoto's struma	59×30	60×30×30	− 1
13	Nodular thyroid	18×11	15×15	−12
14	Nodular thyroid	23×19	25×20×10	−14
15	Nodular thyroid	40×20	28×20	+54
16	Papillary carcinoma	24×22	26×15×8	+35
17	Adenomatoid goiter	39×21	33×23	+ 8
			Mean % difference	20.6
			±S.D.	16.1

measured dimensions of these spots. The scanners are thus capable of excellent resolution under ideal conditions down to 0.5 cm. in small organ phantoms. The reliability of a scanner under the conditions of actual clinical use cannot be based solely on such phantom studies. The observed differences found here between *in vivo* scans and *in vitro* measurements establish some measure for judgment of the reliability of actual organ scans.

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RADIATION INDUCED HEPATIC INJURY*

ITS DETECTION BY SCINTILLATION SCANNING

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THE delivery of high levels of ionizing radiation to the liver occurs in two general radiotherapeutic settings. In the first, hepatic radiation is employed to control intrahepatic neoplasia; in the second, it is not primarily intended, but results inevitably from the organ's proximity to the lesion under treatment. Regional hepatic irradiation takes place during treatment of neoplasms in the lower zones of the lungs, in the mediastinum, in the kidney and in the pancreas as well as during radiotherapeutic induction of gastric achlorhydria; it is unavoidable if the primary purpose of treatment is to be accomplished.

Whereas careful consideration is now given to incidental irradiation of the kidney, there is no evidence of similar concern for the hepatic radiation dose during treatment of perihepatic lesions. There appear to be two explanations for this difference: the fact that seldom is the entire liver irradiated incidentally, and the widespread belief that the liver is a relatively radioresistant organ. The concept of hepatic radioinsensitivity originated in early clinical observations and investigations, summarized by Ellinger,[5] in which no significant sequelae of therapeutic hepatic irradiation were found. Ellinger stated that the liver was far more resistant to local than whole body irradiation. However, in reviewing the subject 24 years ago, Warren[13] observed that the liver was assumed to be relatively resistant to radiation injury "without much conclusive evidence." He noted reports of postirradiation hepatic necrosis and fibrosis, but concluded that the degree of hepatic radiosensitivity had not been established. Examples of necrosis and fibrosis of the liver in patients dying shortly after doses in excess of 5,000 r were described by Brick,[3] but none was found in patients dying more than 5 years after hepatic irradiation.

New histologic and clinical evidence of hepatic radiation injury has appeared recently. Ogata *et al.*[10] observed radiation damage in hepatic parenchymal and reticuloendothelial tissue, arterioles and capsule in 3 patients who had received high levels of cobalt 60 radiation for carcinoma of the lower zones of the lung. The gross pathologic changes, confined to the irradiated superior portion of the liver, resembled chronic congestion. Histologic findings included desmoplasia, arterial hyalinization, sinusoidal engorgement and atrophy and loss of polygonal cells. In 1965, Ingold *et al.*[7] reported a clinical condition, which they have named "radiation hepatitis," occurring in patients after therapeutic irradiation of the entire liver. This syndrome, marked by hepatomegaly, ascites and jaundice, was observed in 13 patients. It was usually transient but progressed to hepatic failure and death in 3 patients.

In the past decade, a number of studies employing modern radiopharmaceutic and histochemical techniques has helped clarify and quantitate the nature of radiation induced hepatic injury. The earlier investigations of the production of "fatty liver" by whole body radiation have been extended to implicate damage to specific hepatic enzyme systems.[1] Postirradiation inhibition of hepatic reticuloendothelial phagocytosis has been established.[2] Weinbren *et al.*[14] have shown that the normally great capability of the liver to regenerate

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can be suppressed by radiation. Looney *et al.*[8] observed marked inhibition of deoxyribonucleic acid synthesis after local hepatic irradiation. In many of these studies the radiation doses employed were extremely high, resulting in necrosis. However, in 1965, de Mignard *et al.*[9] studied the effect on the rat liver of 90–600 r given in one dose (thus approximating the clinical radiotherapeutic situation) and found well-defined histologic and histochemical changes in parenchymal and reticuloendothelial cells. The radiation effects were transient, having disappeared after 6 weeks. These experimental data are in agreement with the clinical conclusion of Ingold *et al.*[7] that the liver is not a radioresistant organ.

Application of photoscanning techniques to the detection of radiation induced hepatic injury was reported in 1965 by Usselman,[12] who performed serial scans of the liver in 4 patients receiving 2 mev. irradi-

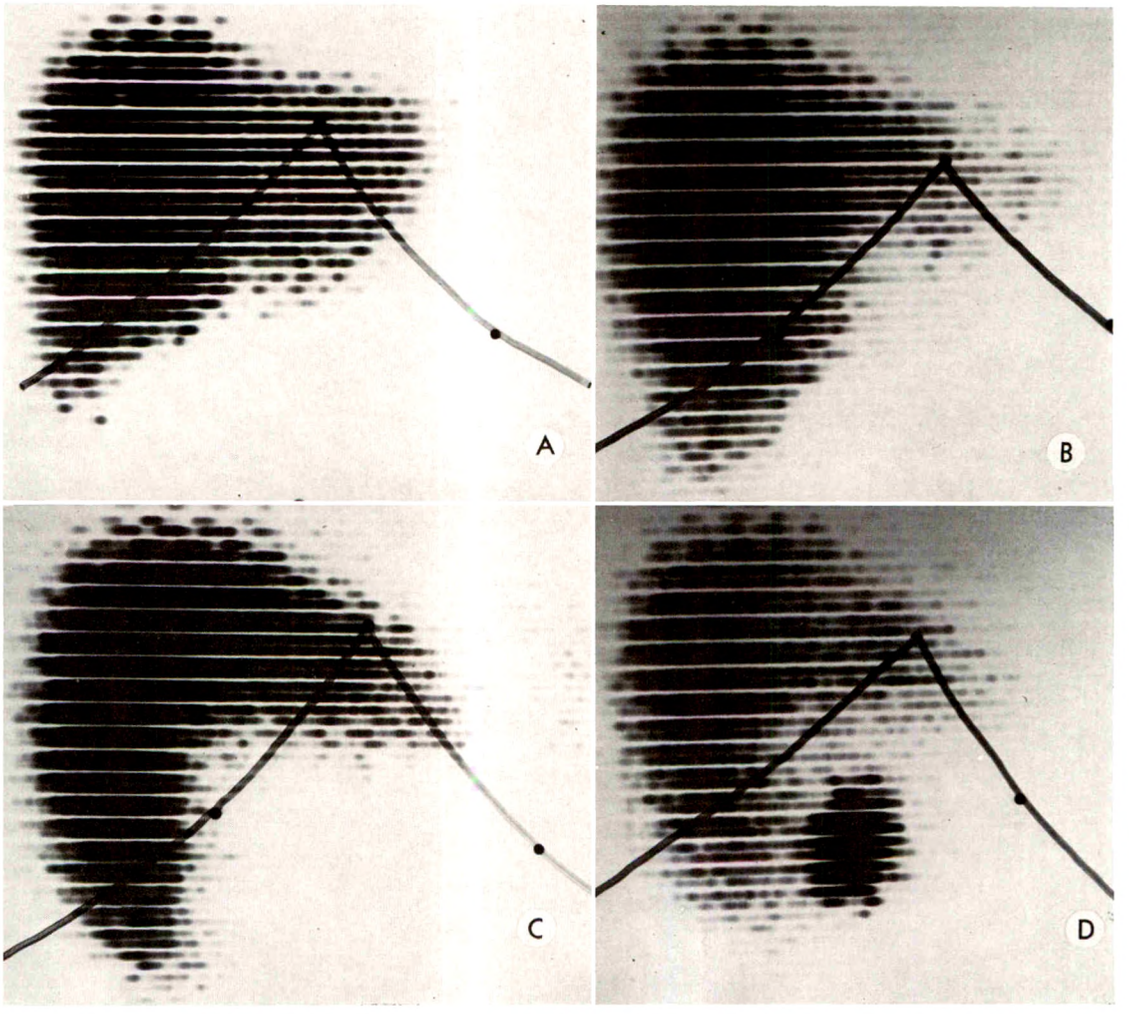


FIG. 1. Case. 1. (PH #101-21-74). *Hepatic irradiation (tissue dose 2,400 r/20 days) for metastases from carcinoma of breast.* (*A*) Normal hepatic scan (Au^{198} colloid) 5 years after mastectomy. (*B*) One year later scan (Au^{198} colloid) demonstrates hepatomegaly and space occupying lesions in left lobe. Radiation therapy was begun 7 days later. (*C*) Forty-eight days after completion of treatment, follow-up scan (Au^{198} colloid) shows absence of phagocytosis in the irradiated area. (*D*) Scan following administration of I^{131} rose bengal discloses subtotal suppression of polygonal cell function in irradiated tissue 63 days after treatment. The ovoid collection of activity superimposed on the nonfunctioning area represents radioactive bile within the gallbladder.

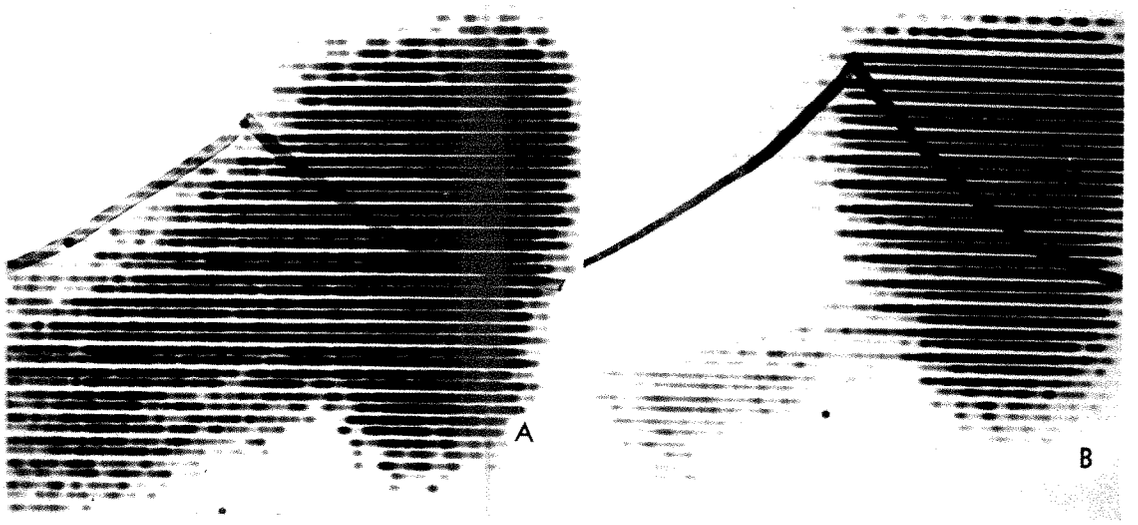


Fig. 2. Case 2. (PH #155-95-03). *Hepatic irradiation (tissue dose 3,600 r/17 days) for primary carcinoma of liver.* (*A*) Initial scan (Au^{198} colloid) demonstrates marked hepatomegaly and a large mass superiorly in the right lobe with smaller lesions inferiorly. Radiation therapy was begun 22 days later. (*B*) Subtotal to total suppression of phagocytosis in the irradiated area is evident on repeat scan (Au^{198} colloid) 18 days after completion of treatment.

ation of the mediastinum for control of testicular carcinoma. In these patients, the left hepatic lobe was included in the treated area. In each case, the preliminary scan of the liver was normal, but after completion of treatment, the follow-up scan showed reduced or absent radioactivity in the left lobe. Usselman concluded that the liver was more susceptible to external irradiation than generally realized.

Our experience with hepatic scanning as an indicator of radiation induced hepatic injury is based on observations in 6 patients who received intentional or incidental irradiation of the liver. In none were sequelae of hepatic irradiation clinically evident.

REPORT OF CASES

Case 1. A 46 year old white female underwent right radical mastectomy in 1956 for mammary carcinoma. Axillary contents were negative for metastases, but several years later osseous and pulmonary metastases appeared. Oophorectomy was performed in 1961; at that time the liver was not palpable, the serum alkaline phosphatase was 6 King-Armstrong units and the hepatic scan (Au^{198} colloid) was normal (Fig. 1*A*). In 1962, metastases had progressed and the liver was palpable. The alkaline phosphatase was 21 King-Armstrong units. A repeat scan (Au^{198} colloid) showed hepatomegaly with evidence of space occupying lesions in the left lobe (Fig. 1*B*). A course of betatron radiation was given, with delivery of 2,400 r tissue dose in 20 days to the central left lateral portions of the liver. Forty-eight days later, a repeat scan (Au^{198} colloid) showed no radioactivity in a sharply defined area of the liver corresponding to location of the treatment portals (Fig. 1*C*). The final scan, employing I^{131} rose bengal, also revealed no radioactivity in the irradiated region 9 weeks after treatment (Fig. 1*D*). The patient was later lost to follow-up.

Comment. Serial scanning demonstrated complete suppression of both reticuloendothelial and parenchymal cell function within the irradiated sector of the liver, 7 and 9 weeks after treatment.

Case 2. A 50 year old Oriental male was admitted for fatigue, weight loss and 5 cm. hepatomegaly with onset 18 months earlier. The serum alkaline phosphatase was 13 King-Armstrong units. Percutaneous liver biopsy disclosed malignant hepatoma. A hepatic scan (Au^{198} colloid) showed a large mass in the right hepatic lobe (Fig. 2*A*). At laparotomy, the tumor was multicentric, with scattered, small nodules in addition to the dominant mass de-

tected preoperatively. Supervoltage radiation was given to the right lobe of the liver, with delivery of 3,600 r tissue dose in 17 days. Eighteen days later, a hepatic scan (Au^{198} colloid) disclosed absence of radioactivity in the irradiated area (Fig. 2*B*). The patient went elsewhere for further care.

Comment. The well-defined zone of absent radioactivity on the post-treatment scan corresponded to the position of the treatment portals and indicated severe suppression of reticuloendothelial phagocytosis.

CASE 3. A 44 year old white female underwent anterior resection for adenocarcinoma of the sigmoid colon in 1959. In 1963, an apparently solitary metastasis in the upper zone of the left lung was resected. In 1964, hepatomegaly was noted. A scan of the liver disclosed a large mass in the right lobe (Fig. 3*A*). Five months later the liver and the intrahepatic mass were larger (Fig. 3*B*); the serum alkaline phosphatase was 12 King-Armstrong units. Although histologic proof was lacking, supervoltage irradiation of the right hepatic lobe (2,900 r tissue dose in 21 days) was performed. A repeat scan 11 days after treatment showed

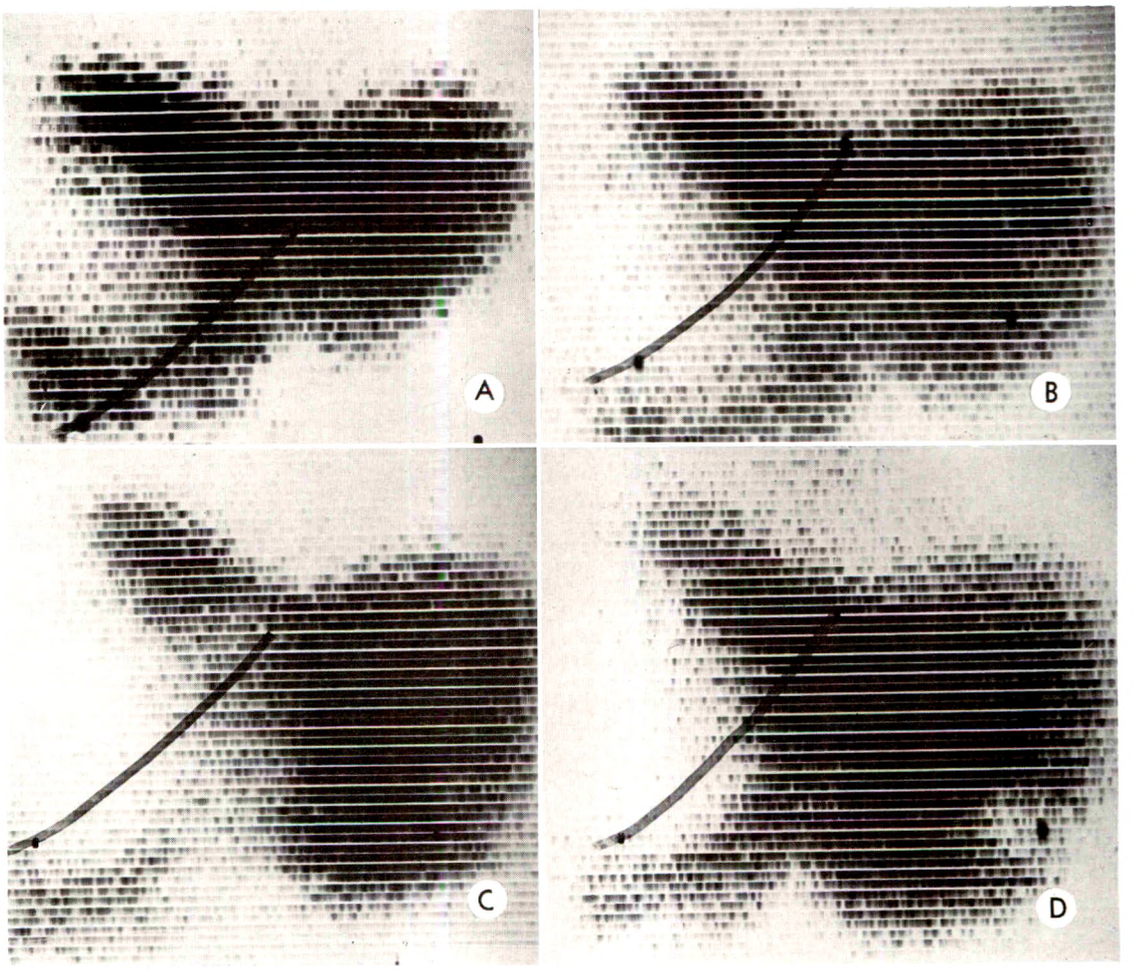


FIG. 3. Case 3. (PH #144-54-65). *Hepatic irradiation (tissue dose 2,900 r/21 days) for massive metastasis from carcinoma of colon.* (*A*) Initial scan shows hepatomegaly and a large mass in the right lobe. (*B*) Five months later repeat scan demonstrates further enlargement of liver and mass; smaller lesions are suggested in the left lobe. Radiation therapy was begun 24 hours later. (*C*) Eleven days after completion of treatment, scan reveals suppressed phagocytosis in hepatic tissue medial and inferior to the mass. (*D*) Ninety-eight days after completion of treatment, normal phagocytosis has reappeared in the irradiated area. The mass is virtually unchanged and definite lesions are seen in the left lobe. Au^{198} colloid was used for all scans.

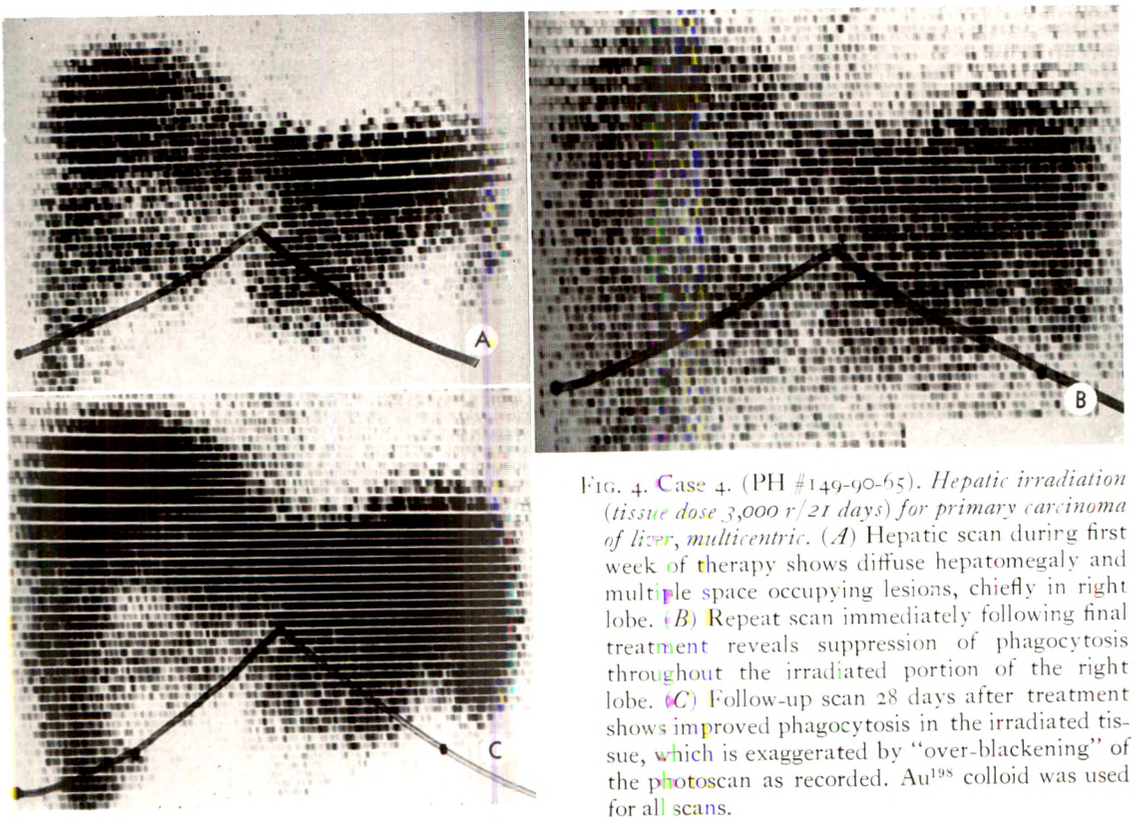


Fig. 4. Case 4. (PH #149-90-65). *Hepatic irradiation (tissue dose 3,000 r/21 days) for primary carcinoma of liver, multicentric.* (*A*) Hepatic scan during first week of therapy shows diffuse hepatomegaly and multiple space occupying lesions, chiefly in right lobe. (*B*) Repeat scan immediately following final treatment reveals suppression of phagocytosis throughout the irradiated portion of the right lobe. (*C*) Follow-up scan 28 days after treatment shows improved phagocytosis in the irradiated tissue, which is exaggerated by "over-blackening" of the photoscan as recorded. Au^{198} colloid was used for all scans.

locally reduced radioactivity in hepatic tissue, surrounding the lesion. Fourteen weeks later, a normal level of radioactivity was present in the irradiated tissue (Fig. 3*D*). Au^{198} colloid was used for all scans.

Comment. In this patient, radiation induced suppression of reticuloendothelial phagocytosis was partial and transient, clearing prior to the 14th week post irradiation.

Case 4. A 58 year old Negro male developed progressive hepatomegaly after admission for right-sided pleurisy. The serum alkaline phosphatase rose from 21 to 42 King-Armstrong units. Closed hepatic biopsy disclosed only minimal fibrosis but a scan of the liver (Fig. 4*A*) showed several masses. Open hepatic biopsy revealed necrotic tumor, histologically a malignant hepatoma. Supervoltage therapy was administered to the central and right portions of the liver, with delivery of 3,000 r tissue dose in 3 weeks. A scan of the liver on the final day of treatment (Fig. 4*B*) showed uniformly diminished radioactivity in functioning tissue in the irradiated area; this finding was less marked 4 weeks later, although the quality of the scan (Fig. 4*C*) would minimize any difference. At autopsy 5 weeks later an enlarged liver, containing multiple nodules of necrotic hepatoma, was found. Microscopically, the hepatic parenchyma adjacent to the neoplasm was normal apart from compression.

Comment. In this patient transient partial suppression of reticuloendothelial function was demonstrated immediately and 4 weeks after hepatic irradiation. There were no histologic findings attributable to radiation injury 9 weeks after treatment.

Case 5. A 32 year old white male underwent orchiectomy in 1961 for seminoma with involvement of retroperitoneal lymph nodes. Postoperative radiation therapy was given to the pelvic region, and a recurrence in the right inguinal area 1 year later was treated by radical groin dissection and irradiation. One year later a lower abdominal mass appeared but regressed after local radiation therapy. The serum alkaline phosphatase then was 10 King-Armstrong

units. In 1964 hepatomegaly was noted, the alkaline phosphatase was 15 King-Armstrong units and a mass was shown in the right hepatic lobe by scanning (Fig. 5*A*). The patient received hepatic irradiation at another institution, with delivery of 3,500 r tissue dose to the right lobe by a cobalt 60 beam. Four weeks after treatment, a repeat scan showed significantly diminished radioactivity in the irradiated area and shrinkage of the presumed metastasis (Fig. 5*B*). Twelve weeks after treatment, there was normal distribution of radioactivity in the right lobe (Fig. 5*C*); subsequent scans have shown no change.

Comment. These findings suggest that hepatic reticuloendothelial tissue is less sensitive than metastatic seminoma to ionizing radiation. The radiation effect disappeared between 4 and 12 weeks after treatment.

CASE 6. A $2\frac{1}{2}$ year old white male underwent nephrectomy in 1964 for a right renal mass which histologically was Wilms' tumor. The tumor bed was irradiated postoperatively (3,000 r tissue dose in 3 weeks) by means of a betatron beam. Because of its proximity, the central inferior portion of the liver was necessarily included in the area of treatment. Thirty-three days after irradiation, a scan showed a localized area of diminished radioactivity in the inferio-central zone of the liver, which was enlarged. This area corresponded in position to that of the radiation portals. A repeat scan 14 weeks after irradiation and following treatment with vincristin showed decreased hepatic size and normal distribution of radioactivity in the inferio-central region.

Comment. Although a pretreatment scan was not obtained in this patient, transient

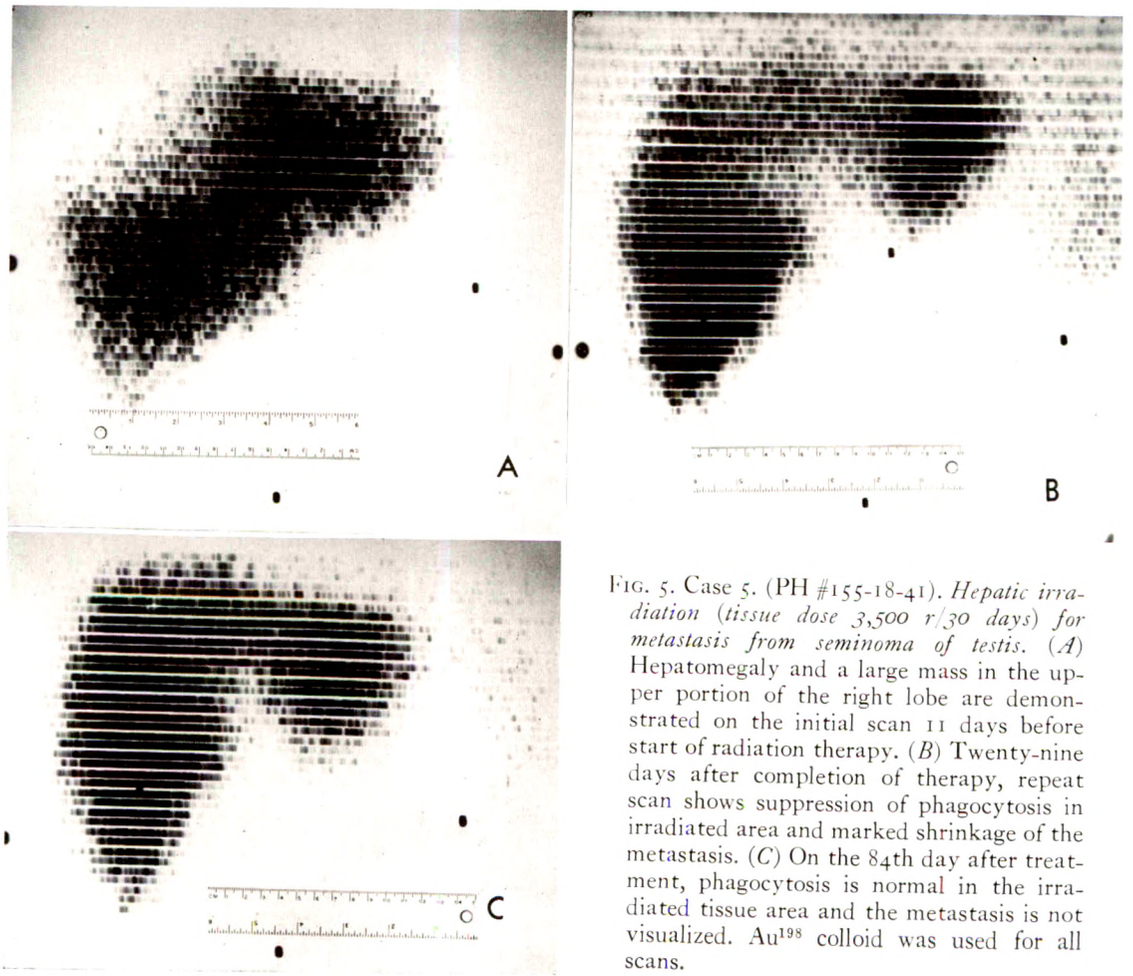


FIG. 5. Case 5. (PH #155-18-41). *Hepatic irradiation (tissue dose 3,500 r/30 days) for metastasis from seminoma of testis.* (*A*) Hepatomegaly and a large mass in the upper portion of the right lobe are demonstrated on the initial scan 11 days before start of radiation therapy. (*B*) Twenty-nine days after completion of therapy, repeat scan shows suppression of phagocytosis in irradiated area and marked shrinkage of the metastasis. (*C*) On the 84th day after treatment, phagocytosis is normal in the irradiated tissue area and the metastasis is not visualized. Au^{198} colloid was used for all scans.

TABLE I

TREATMENT FACTORS USED FOR HEPATIC IRRADIATION

Case	Indication	Mev.	Target-Skin Distance (cm.)	Treatment Portals	Tissue Dose (mid-line)	Over-all Time	No. of Treatments	Equivalent Single and 6 week Doses	Effect
1 (VZ)	Metastatic carcinoma	22.5	120	12×15 cm. opposing	2,400 r	20 days	6	1,400 rad (single) 4,400 rad (6 weeks)	Total suppression of RES *48 days post irradiation; subtotal suppression of polygonal cells 63 days post irradiation
2 (EW)	Hepatoma	22.5	120	12×15 cm. opposing	3,500 r	17 days	6	1,830 rad (single) 5,500 rad (6 weeks)	Total suppression of RES 18 days post irradiation
3 (MF)	Metastatic carcinoma	22.5	120	15×15 cm. opposing	2,900 r	21 days	15	1,300 rad (single) 3,900 rad (6 weeks)	Partial suppression of RES 11 days post irradiation; normal RES function 98 days post irradiation
4 (EB)	Hepatoma	22.5	120	15×15 cm. opposing	3,000 r	21 days	15	1,340 rad (single) 4,000 rad (6 weeks)	Partial suppression of RES on final day of treatment; less marked 29 days post irradiation
5** (OP)	Metastatic eminoma	1.2	?	?	3,500 r	30 days	22	1,340 rad (single) 4,000 rad (6 weeks)	Partial suppression of RES 29 days post irradiation; apparently normal RES function at 84 days; normal function 187 days post irradiation
6 (JM)	Incidental to tumor bed irradiation	22.5	80	10×10 cm. opposing	3,000 r	21 days	15	1,340 rad (single) 4,000 rad (6 weeks)	Partial suppression of RES 35 days post irradiation; normal RES function 106 days post irradiation

* Reticuloendothelial system.
** Treated elsewhere.

impairment of reticuloendothelial function in the irradiated sector of the liver suggests that radiation induced injury had been present.

TREATMENT DATA

Five patients (Cases 1–4 and 6) received 22.5 mev. betatron radiation to the liver. The 6th patient (Case 5) was treated elsewhere with a cobalt 60 beam; the size of the portal(s) and target-skin distance are not known. The treatment factors employed are listed in Table 1.

The equivalent-dose nomogram of Burns,[4] as modified by Shuttleworth and Fowler,[11] was used to provide a standardized basis for comparison of dose and effect (Fig. 6). Table 1 shows the calculated radiobiologically equivalent single and 6 week (30 treatment) dose for each case. The nomogram is considered more accurate for calculating the latter dose.

DISCUSSION

The findings in this group of patients agree with other recent clinical and investigative data[1,2,7–10,12,14] which indicate that the liver is relatively radiosensitive. Our results confirm Usselman's[12] observation that scintillation scanning of the liver can detect radiation induced hepatic injury. By selection of the appropriate radiopharmaceutical, the status of hepatic parenchymal or reticuloendothelial function can be determined. The potential clinical utility of this finding is apparent.

In our patients, the scan became positive for radiation induced injury after doses of 3,900–5,500 rad (equivalent 6 week dose). Totally suppressed function in the ir-

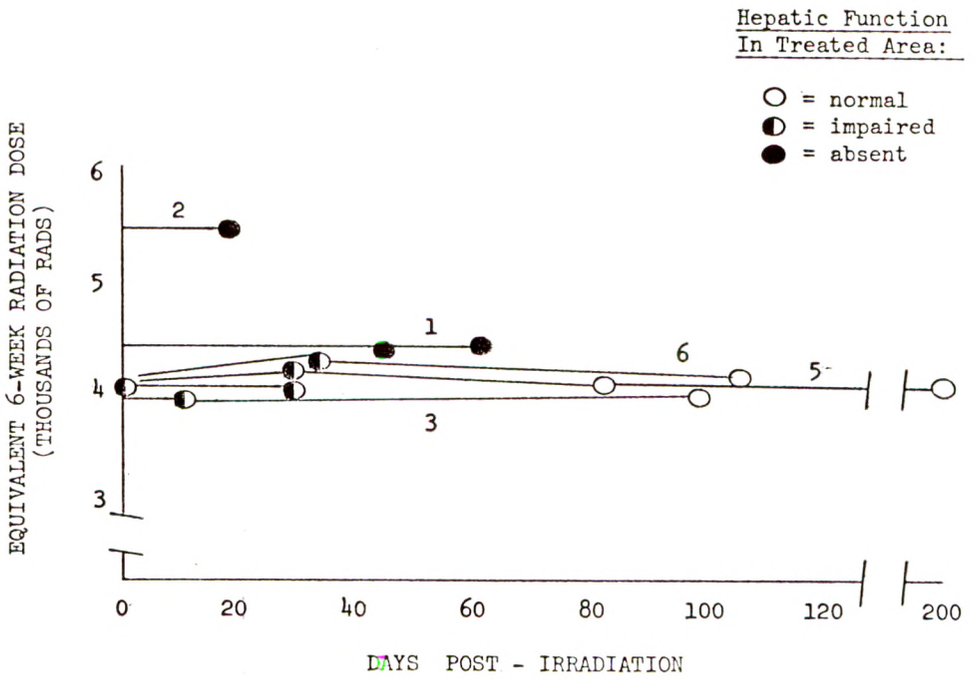


FIG. 6. *Relationship of hepatic radiation dose to intensity and duration of hepatic functional injury.* The actual radiation dose is expressed in terms of its calculated radiobiologically equivalent 6 week counterpart.[4,11] The latter dose is given by the level at which the "time line" of each case intersects the ordinate. Slight vertical displacement of several points was necessary to show clustered data. The number adjacent to each "time line" indicates the corresponding case number.

radiated area was observed in the 2 patients receiving the highest doses. However, in 1 the dose was not significantly greater than that given the remaining 4 patients in whom function was only partly suppressed. This may indicate individual variation in hepatic radiosensitivity. Ingold *et al.*[7] have concluded on clinical grounds that 3,000–3,500 rad to the entire liver in 3–4 weeks was probably safe. In Usselman's[12] patients, in whom hepatic injury was apparently subclinical, doses of 3,400 rad (in 23 days) to 4,000 rad (in 5 weeks) were delivered to the left lobe of the liver.

Our data are insufficient to determine accurately the duration of radiation induced hepatic injury. They suggest that the impairment of function disappears prior to the 12th–15th week post irradiation. Follow-up limitations prevented prolonged serial scanning in the 2 patients exhibiting complete local functional suppression in the irradiated hepatic sector 2.5 and 9 weeks after treatment, respectively.

During the period when radiation induced hepatic injury was evident by scanning, no patient presented clinical findings suggestive of radiation hepatitis. It is possible that intrahepatic neoplasia may have obscured manifestations of mild hepatic injury. Serial batteries of hepatic function tests, which might have detected subclinical injury, were not obtained. Autopsy in 1 patient (Case 4) failed to reveal histologic evidence of radiation injury. No patient presented evidence of preexisting cirrhosis or other diffuse hepatic parenchymal disease.

The significance of subclinical radiation induced hepatic injury merits investigation. Fischer and Fischer[6] have demonstrated that reticuloendothelial system (RES) blockade in rats favors the development of hepatic metastases of Walker 256

carcinoma. It would be desirable to learn the extent to which the reserve functional capacity of the liver offsets the insult of localized irradiation. Presumably, this would depend on the existing functional status of the liver and its blood supply, the volume of hepatic tissue irradiated, the intensity and duration of functional impairment and the nature of any challenge.

The sensitivity of the hepatic scintillation scan in detecting radiation induced hepatic injury has not been established. The basis of the scan is integrity of the physiologic mechanisms by which radiopharmaceuticals are concentrated in the liver: phagocytosis of colloids by Kupffer cells and active transport of agents such as I^{131} rose bengal by polygonal cells. Regional cellular injury, displacement or death appear as areas of diminished or absent radioactivity. The limitations of the hepatic scan in detecting such areas when small or deeply situated are well known. Nevertheless, it is presently the only means short of biopsy by which regional impairment of hepatic function is clinically demonstrable. Quantitation of scanning data would appear likely to increase its sensitivity and thus its clinical value in the management of patients undergoing hepatic irradiation.

The findings described in this report should be of interest to the radiotherapist and may serve to stimulate corroborative clinical studies to determine more precisely the incidence, duration, dose dependency and clinical significance of radiation induced hepatic injury. It is evident that the liver must be regarded as a relatively radiosensitive organ.

SUMMARY

1. Radiation induced suppression of hepatic reticuloendothelial function was demonstrated by scintillation scanning in 6 patients undergoing therapeutic irradiation of the liver. In the 1 patient so tested, suppressed hepatocellular function was also demonstrated.

2. Evidence of injury to the liver was the *de novo* appearance of a well defined area of diminished or absent radioactivity on the scintillation scan, corresponding to the position of the radiation portals in each case.

3. In 3 patients, reappearance of normal function was observed 84–106 days post irradiation. Follow-up of the remaining patients was limited to shorter periods.

4. There were no clinical findings attributable to radiation induced hepatic injury.

5. These data are additional evidence that the liver is a relatively radiosensitive organ.

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Vol. 99, No. 2

COLLOIDAL THORIUM DIOXIDE (THOROTRAST) IN RADIOLOGY WITH EMPHASIS ON HEPATIC CANCEROGENESIS

A CASE REPORT OF OCCLUDED CAROTID AND JUGULAR VESSELS WITH NERVE INJURIES AND A CASE OF HEPATOMA, 27 AND 33 YEARS AFTER ITS ADMINISTRATION

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THE colloidal form of thorium dioxide was first introduced into diagnostic radiology in 1928 by Blühbaum and associates.[4] After the report about its use for visualization of liver and spleen (hepatolienography) by Radt,[40] it gained wide utilization in a variety of diagnostic procedures. The heavy thorium atom in this preparation makes it a very dense contrast material, highly desirable in roentgenography.

The main contribution of this material, however, was considered to be the excellent roentgenographic visualization of the liver and spleen due to the specific uptake of this colloid by the reticuloendothelial system in these organs. Thorotrast became extremely valuable in gastric cancer patients where liver metastases were suspected.[11,43] There were enthusiastic supporters of this method[21] as well as those who voiced precautions in its use. Huguenin *et al.*[18] produced hepatitis and cirrhosis in experimental animals. Lambin[24] produced aplastic type of anemia experimentally. In 1932, the Council on Pharmacy and Chemistry of the American Medical Association[5] condemned the intravenous use of thorotrast for roentgenographic purposes. Pohle and Richie[39] concluded from their studies on rabbits that thorotrast should be used only on incurable cases because of its toxic effect on the liver. Ericksen and Rigler[11] emphasized the potential dangers of this preparation due to its radioactivity. The damage it causes may become evident only after several years have passed by. Later Rigler and associates[43] recommended the reduction of the dose from the usual 0.8 cc. per kg. of body weight[21,40] to 0.6 cc. per kg. They also recommended that the intravenous use of thorotrast should be confined to older individuals suffering from very grave diseases. The danger of thorium dioxide causing malignancies was shown in experimental animals by Roussy and his co-workers[49] in 1934 and by Selbie[54] in 1936. The first report about a malignant neoplasm in a patient, an endothelial cell sarcoma of the liver, was published in 1947 by MacMahon *et al.*[27] This occurred 12 years after the injection of thorotrast.

Due to the fact that the usage of colloidal thorium dioxide spread to almost every possible procedure, late reports show a variety of malignant neoplasms occurring in the organs and tissue where this material was deposited. Several reports have been published on carcinoma which developed some 10 to 20 years after thorotrast was instilled into the paranasal sinuses.[12] Similarly, development of carcinomas has been reported, for instance, in kidneys after urography, in eyelids after dacryocystography, in bronchi after bronchography, in seminal vesicles after urethrovesiculography, and sarcomas in the kidneys and peritoneum.[9,57] Kyle *et al.*[23] reported a case of meningioma which developed 24 years after thorotrast ventriculography. Maltby[28] de-

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FIG. 1. Case 1. Site of thorotrast extravasation 27 years after an attempted carotid angiography.

scribed 3 cases of severe progressive deleterious cauda equina syndrome resulting from thorotrast myelography.

The once popular use of thorotrast in carotid angiography produced, decades later, granulomas ("thorotrastomas") at the site of the injection where extravasation had occurred. This has caused serious sequelae such as paralysis of the cranial and sympathetic nerves on the neck, and obliteration of the jugular and carotid vessels.[1,3,5,17,35] Also necrosis of the pharynx and development of neurofibrosarcoma[3] and fibroblastosarcoma[9] at the site of extravasation have been reported.

We are adding to the thorotrast literature a case in which the severe thorotrast-induced granulomatous desmoplastic reaction caused complete obliteration of the common carotid artery with nerve damage.

REPORT OF A CASE

CASE 1. O.G., a 60 year old white male, was admitted to the University of Minnesota Hospital in the spring of 1965. The gathered medical history revealed that in 1936, while working, tiny metallic foreign bodies entered his right cervical region. A swelling developed in that area and the patient could hear his heartbeat pounding there. A bruit also was reported to have been present. In 1938, right sided carotid angiography was attempted, resulting in extravasation of thorotrast. The bruit disappeared about 1 year later.

Beginning in 1945, the patient noticed a slowly increasing mass on the right side of his neck which finally brought him to North Memorial Hospital. Exploratory surgery was done in January, 1965, with resultant prolonged drainage of an abscess cavity. The past history also showed that the patient had hypothyroidism needing 4 grains of thyroid extract daily

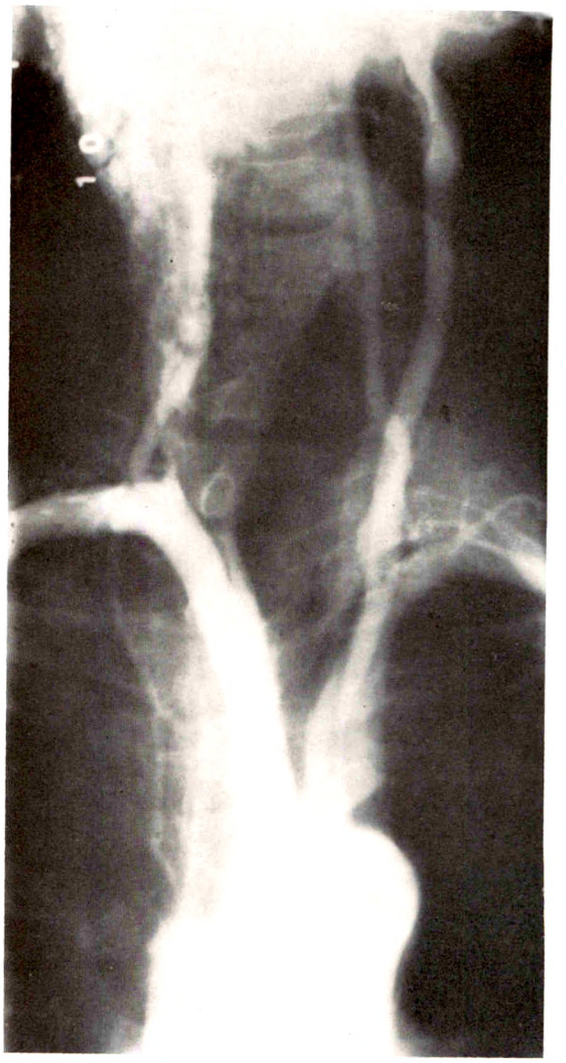


FIG. 2. Case 1. Retrograde aortogram. Extravasated thorotrast has caused complete obstruction of the right carotid artery (see text).

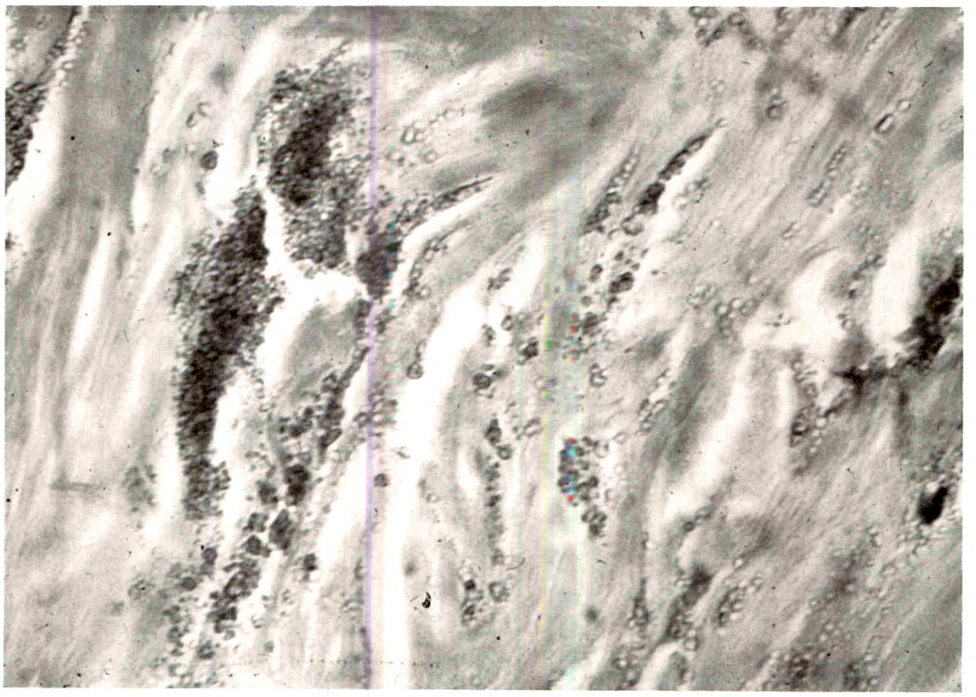


Fig. 3. Case 1. Microphotograph of the cervical "thorotrastoma." Refractile thorotrast granules are seen embedded in dense fibrous tissue.

since 1963. On admission to the University of Minnesota Hospital, the patient had two fistulous tracts from the mass on the right side of his neck. A coagulase negative strain of staphylococcus was isolated from the foul smelling drainage material. The patient had a right sided Horner's syndrome, paralysis of the right vocal cord with paresis of the ninth to twelfth cranial nerves on the same side. Total and differential white blood cell count, hemoglobin, and urinalysis were essentially normal except for the presence of 1 plus albumin in the latter. The serum proteins and bromsulphalein test were normal. The roentgenogram of the chest revealed no abnormalities.

Roentgenograms of the neck (Fig. 1) showed a large dense irregular opacity over the right carotid area, extending to the base of the skull and down to the lower neck. A needle-shaped foreign body was noticed lateral to the right spinosal foramen. The appearance of this wide, streaky shadow is characteristic of extravasated thorotrast. Cinefluoroscopy with barium swallow showed a deviation of the pharynx to the left. A retrograde aortogram of the aortic arch demonstrated a complete occlusion of the right common carotid artery with a short proximal stump (Fig. 2).

During surgery, a mass was found along the great vessels of the neck, extending up to the base of the skull and to the nasopharyngeal wall posteriorly, which was filled with white chalky granules surrounded by a firm, irregular, fibrous wall. This mass was excised by sharp dissection. The obliterated common carotid artery was removed; the internal jugular vein could not be identified.

Microscopic examination showed very dense, hyalinized fibrous tissue with calcifications. Refractile thorotrast granules were seen intracellularly as well as in aggregates embedded in the fibrous tissue (Fig. 3). In places, collections of lymphocytes were seen.

A microradiograph (Fig. 4) demonstrated well the thorotrast granules due to their high absorption coefficient for the utilized low 5 kv. roentgen rays in a 50 μ vacuum chamber.

COMMENT

The time interval between the administration of the colloidal thorium dioxide and the diagnosis of malignancies has been generally 12 to 35 years. The total number of reported malignancies due to thorotrast administration was 37 in 1960.[2] In 1961, Suckow *et al.*[57] gave a total number of 43 reported malignancies that had developed 12

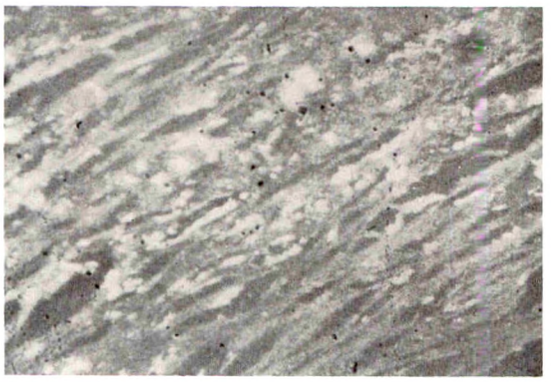


FIG. 4. Case 1. Microradiograph of the cervical "thorotrastoma." Numerous thorotrast aggregates (white) are present among the radiographically less dense collagen bundles.

to 24 years after the administration of colloidal thorium dioxide with only 1 exception in which the interval was a relatively short 3 years. Of the 43, 19 had had thorotrast used in localized body areas, while in the remaining 24 cases the thorotrast had been administered intravascularly. Of the latter, 20 malignancies developed in the liver of which 10 were of the mesenchymal type. These last mentioned 10 cases were reported as: 3 endothelial cell sarcomas, 4 hemangioendotheliomas, 1 angioblastic sarcoma, 1 hemangiosarcoma, and 1 "mesenchymal tumor of the liver." The remaining 10 malignancies of the liver were carcinomas. Five were of the biliary and 5 of the liver cell types. In 1963, Blomberg *et al.*,[3] while following-up 436 patients who had undergone cerebral thorotrast angiography, reported 5 additional hepatic carcinomas, type not specified, and 1 more hemangioendothelioma. Möbius and Lembcke[31] in 1963 showed a total of 30 thorotrast induced liver malignancies including their own 3 cases. Among these were 15 endothelial cell sarcomas, 9 cholangiomas, and 6 hepatomas. In addition to these, we found in the literature[10,38] 2 more cases of biliary type hepatic carcinomas, 1 hepatoma,[15] and 3 hemangioendotheliomas.[16,42,61] Horta *et al.*,[17] in their 1965 follow-up of 1,107 patients in Portugal, who had received thorotrast between 1930 and 1952, reported 22 cases of fatal hemangioendotheliomas of which almost all occurred 20 years or more after the administration of thorotrast. Seventeen patients died from cirrhosis of the liver, 8 due to sequelae of local thorotrast granulomata and 2 due to blood dyscrasias.

Adding together all the thorotrast associated case reports that we have found in the literature, the following breakdown of liver malignancies appears:

Hepatic sarcomas (the majority are reported as hemangioendotheliomas)		41
Hepatic carcinomas (including our case, reported below)		24
The latter can be further divided into:		
Carcinomas of the liver cell type (hepatomas)	8	
Carcinomas of the biliary duct type	11	
Nonspecified[3]	5	
Total liver malignancies		65

The bulk of malignant tumors which occurs in the liver represents sarcomatous degeneration of the reticuloendothelial cells where this long-acting alpha emitter was deposited. This is by no means surprising if one considers the short penetrating power of the alpha particles in the tissue, some 30 to 50 μ. This alpha radiation accounts for more than 90 per cent of the total ionizing energy dissipated in the tissues by thorium and its daughter products.[48] The thorotrast associated liver carcinomas make up only one-half of the number of liver sarcomas.

There appears to be slightly more biliary duct type of carcinomas than those of the hepatic cell type. We were able to find in the available literature only 7 cases of the latter type which together with our case make a total of 8 hepatomas.

REPORT OF A CASE

CASE II. S.M., a 53 year old truck farmer, was admitted to the Minneapolis Veterans Hospital on November 4, 1964. He presented a history of chronic alcoholism and complained about sporadic pains in the right upper quadrant of the abdomen with radiation into the right side of the chest and axilla during the past 5 years. Further investigation revealed that this patient had received in 1932 (33 years ago) a total dose of 100 cc. thorotrast intravenously. That study was conducted to determine the presence of a suspected subdiaphragmatic abscess or other

pathology in the liver. The thorotrast hepatolienograms were reported as normal.

The physical examination when last hospitalized revealed a well developed, fairly well nourished white male in no acute distress. His temperature was 101° F. orally. His slightly tender liver was palpable 8 cm. below the rib cage and had a firm consistency. His white blood cell count was 10,400 with 82 per cent neutrophilic polymorphonuclears; the hemoglobin was 11.7 gm. per cent. The serum bilirubin values were 0.7 mg. per cent and 1.7 mg. per cent as the direct and total amount, respectively; alkaline phosphatase was 42 King-Armstrong units and the albumin globulin ratio was 3.1/3.0. The bromsulphalein test showed 30 per cent retention.

The roentgenograms of the abdomen revealed a reticularly opacified liver and spleen and very dense celiac lymph nodes (Fig. 5 and 6). The small size of the spleen was indicative of severe atrophy. The roentgenograms of the chest showed clear lung fields and a normal heart. However, osteolytic metastases were seen in the ribs.

While in the hospital the patient developed ascites. No malignant cells were found in the clear yellowish intraperitoneal fluid. A splenoportogram was made (Fig. 7) which showed obstruction of the portal vein with collateral

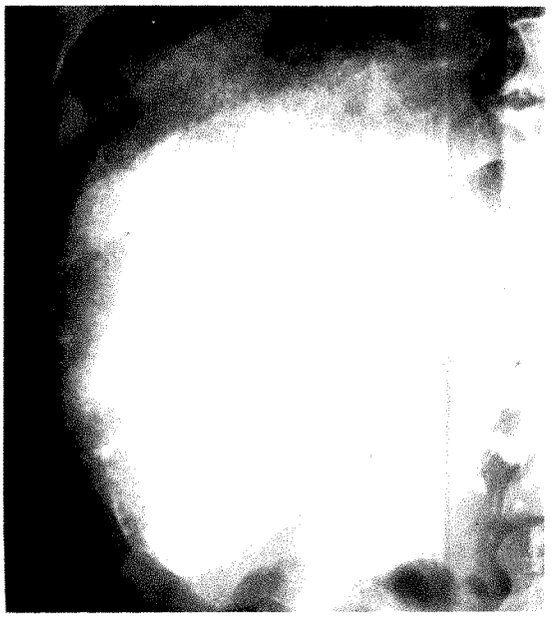


Fig. 5. Case 11. The reticulated lacy opacification of the liver and the very dense regional lymph nodes are characteristic of long term deposition of thorotrast in these organs.



Fig. 6. Case 11. The appearance of the typical small sized, heavily and granularly opacified thorotrast spleen, due to chronic exposure.

circulation through the lower esophageal veins. The very small atrophied spleen was again noted. A splenorenal shunt was performed on November 13, 1964. The portal vein pressures before and after the procedure were recorded as 42 and 34 mm. of mercury, respectively. Multiple liver biopsies showed a marked portal

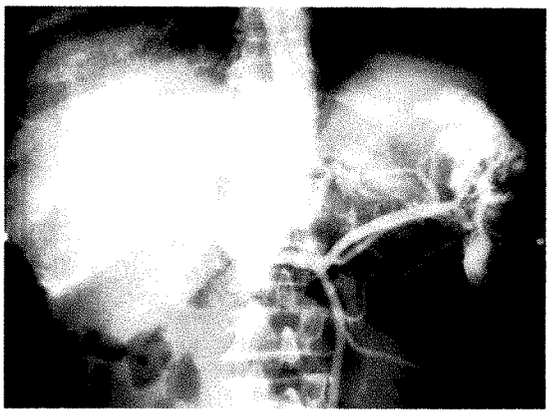


Fig. 7. Case 11. Splenoportogram showing obliteration of the portal vein due to thorotrast cirrhosis. The collateral circulation through the short gastric veins and lower esophageal plexus is seen. The marked atrophy of the spleen and the very heavily opacified regional lymph nodes are additional evidence indicating the existence of an advanced thorotrast liver.



FIG. 8. Case 11. Roentgenogram of the postmortem liver section demonstrates severe cirrhotic changes induced by thorotrast. The extremely dense fibrous tissue and embedded aggregates of thorotrast are the reason for the high contrast found in this roentgenogram.

fibrosis with yellowish-brown granules of thorotrast embedded in connective tissue. One biopsy revealed some changes suspicious of anaplasia of the liver cells. The removed spleen had thorotrast granules in the macrophages. The bulk of it, however, was in the trabeculae. A passive congestion was also evident. Post surgery, the patient had a downhill course with increasing jaundice and edema of the lower extremities. He died on March 3, 1965.

Autopsy. On postmortem examination, the liver weighed 1,930 gm. It showed blunt edges and a thickened Glisson's capsule. The surface of the liver was studded with yellowish-white tumor nodules, the largest collection being at the gallbladder bed area, extending deep into the parenchyma.

A roentgenogram made of a thick slice of liver (Fig. 8) showed a very dense, reticular pattern throughout (compare with Fig. 5), caused by the thorotrast-impregnated connective tissue. The homogenized, dried liver sample gave evidence of radioactivity when measured in a gasflow counter at the Geiger region. The radioactivity was found to be 2.1 times higher than in a similarly prepared sample from the kidney. The latter count was not statistically different from that of the control sample.

Microscopic examination of the liver showed an over-all distortion of the architecture with marked overgrowth of the connective tissue in the portal areas and extending diffusely throughout the parenchyma. Numerous dark-brown aggregates of thorotrast were seen in the connective tissue (Fig. 9). This dark material was also seen scattered diffusely in the Kupffer cells. There was presence of bile stasis and proliferation of the bile ducts in the portal spaces. Areas of malignant liver cells were seen which formed strands and cords. In some places they adopted a pseudoglandular configuration (Fig. 10). The tumor cells showed marked pleomorphism with a large round or oval nucleus with prominent nucleoli. The cytoplasm stained well with eosin. The groups of malignant tumor cells were supported by dense collagenous stroma. Numerous tumor-nodules had necrotic centers.

Metastases which had the same type of tumor cells were found in the medulla and cortex of the kidneys, adrenals, thyroid, ribs, and in the vertebral bodies. The celiac lymph nodes were hard and had a dark brown color. Thorotrast granules were seen in macrophages surrounded by connective tissue. Foreign body granulomas also were present, consisting of epitheloid cells, plasma cells, lymphocytes, and scattered giant cells. The lungs revealed the presence of an extensive bronchopneumonia. Atherosclerotic plaques were found in the coronary arteries.

COMMENT

Autoradiographs were made from sections of tissues. The best results were obtained by using the Kodak AR 10 stripping film with floating technique. The most striking effect of alpha tracks was obtained from the sections of the liver where the thorotrast granules were abundantly present (Fig. 11). For comparison, an autoradiograph was made of the thorotrast itself (Fig. 12). We found the suitable exposure time to be 30 days.

DISCUSSION

Thorium dioxide is a white compound, insoluble in water. It is found in minerals like thoranite together with some 10 per cent of uranium dioxide. The principal source of thorium in the United States is monazite sand. The purified colloidal form of thorium dioxide, which has a brown

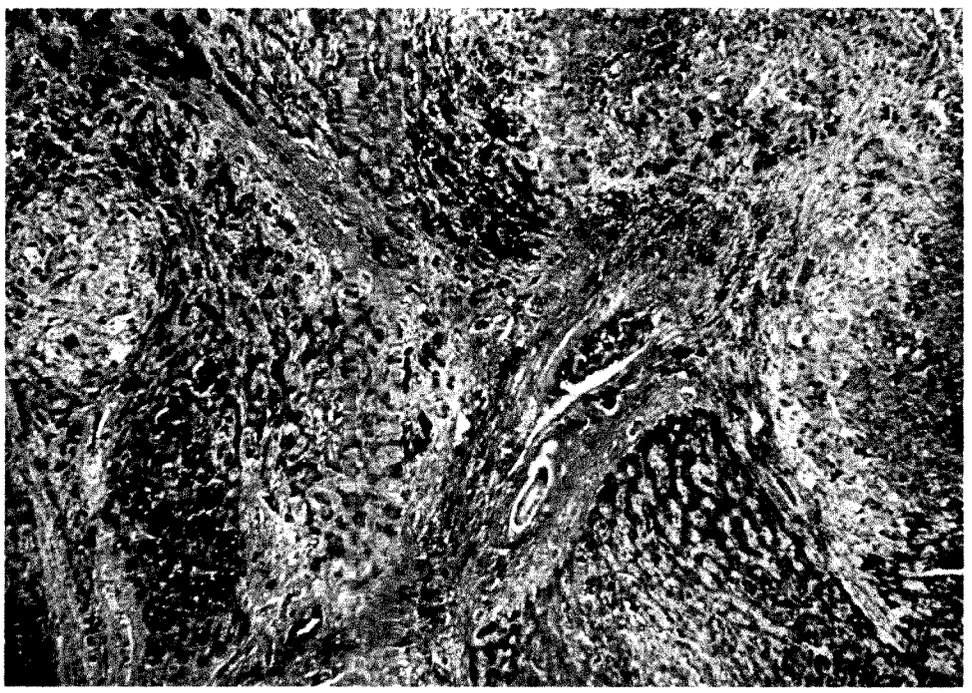


FIG. 9. Case II. Microphotograph of the postmortem liver showing severe portal type of cirrhotic changes. Thorotrast can be recognized as dark aggregates surrounded by fibrous tissue (see text).

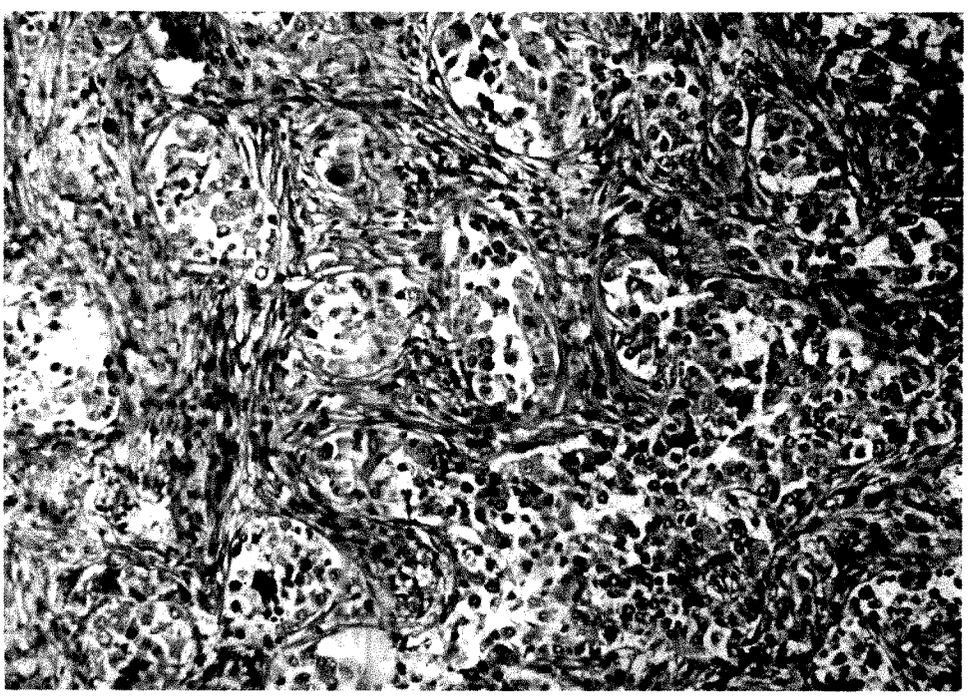


FIG. 10. Case II. Microphotograph of a liver section showing the liver cell type of carcinoma with pseudoglandular configuration and strong desmoplastic reaction.

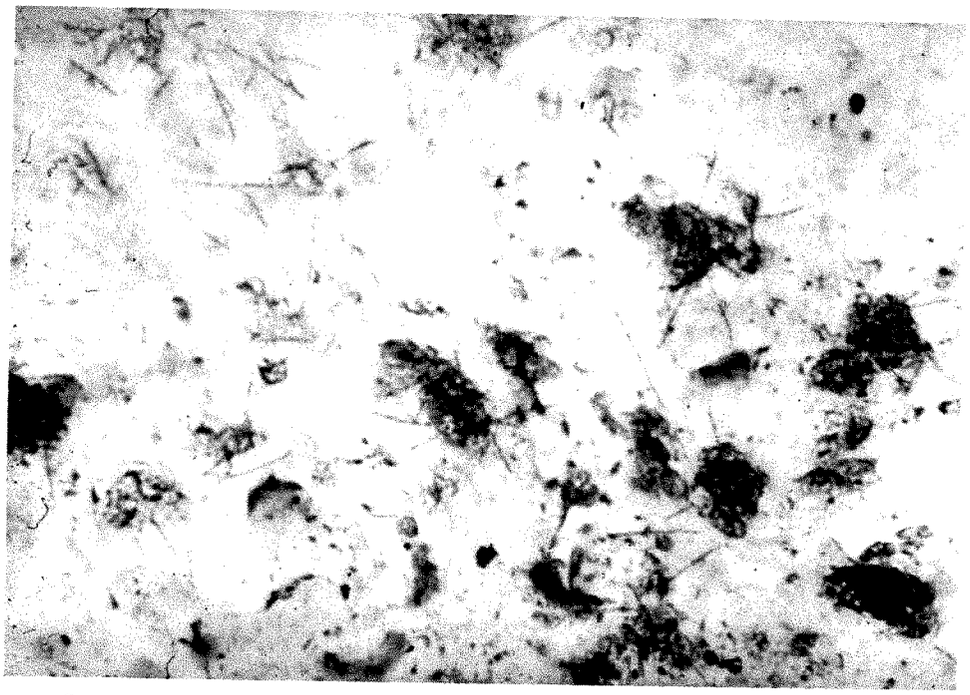


FIG. 11. Case II. Autoradiograph of a liver section demonstrating the heavy, straight alpha tracks which originate in the thorotrast granules.

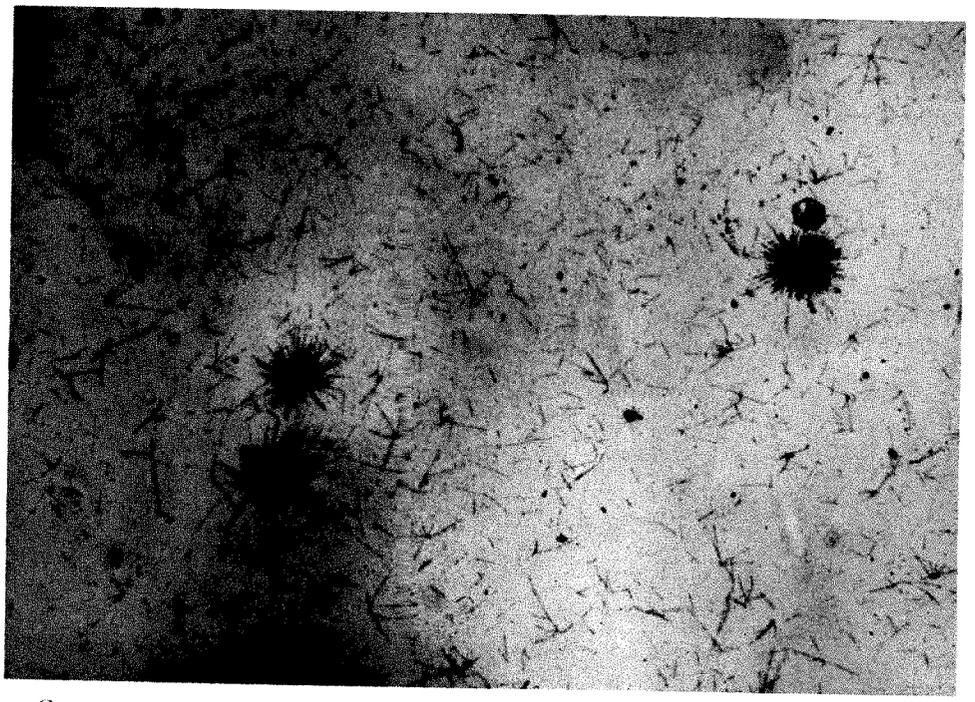


FIG. 12. Case II. Autoradiograph of thorotrast itself. Heavy alpha tracks with star formation are seen. Compare with Figure 11.

color, is known under the name of thorotrast.[29,36] It contains 20–26 per cent of thorium dioxide, dextrin as a stabilizer and a small amount of methylparahydroxybenzoate as a preservative. The nonstabilized colloidal form, umbrathor (Heyden), has been used mainly in gastroenterography and urography. The usual dose of thorotrast in hepatosplenography was 75 cc. and in cerebral angiography about 10 cc.[32] Seventy-five cc. of 20 per cent thorotrast contains 15 gm. thorium dioxide, which has an estimated alpha particle equivalent of 2.1 μg. of radium calculated on the basis of alpha energy.[25] Beta particles contribute only about 9 per cent of the total dissipated energy in the tissues and the gamma radiation about 1 per cent. The physical half life of Th^{232} is 1.4×10^{10} years. The biologic half life of thorotrast is found to be also extremely long, namely some 400 years.[19] The estimated percentage of the retained thorotrast in the organs according to different investigators is: liver 71–73 per cent, spleen 7–17 per cent and bone marrow 6–10 per cent.[25] The latter author examined the autopsied organs of the patients who died 17 and 49 days after the administration of thorotrast. He found thorotrast mainly deposited in the liver, spleen, and bone marrow. The lungs and adrenals contained smaller amounts. Minute amounts were found in all other organs.[25]

In patients who die some 10 or more years after the administration of thorotrast, this substance is found in an aggregate form (Fig. 9 and 11). The spleen is reduced considerably in size due to the destructive effect of the alpha particles. The aggregates, which are best seen in the liver, have quite similar and sometimes even greater size than the range of the alpha particles. This causes considerable amount of selfabsorption of alpha rays in these aggregates.[46]

Thorium 232 has 11 daughter elements (Table 1): 6 are alpha emitters, (3.95 to 10.5 mev.) of which 1 (Bi^{212}) also emits beta particles, 4 are pure beta emitters (0.055 to 2.38 mev.) and the endproduct Pb^{208} is stable. The emission of alpha and beta particles is usually, however, accompanied by gamma radiation (0.04 to 2.61 mev.) which includes the parent Th^{232} (0.059 mev.). The exceptions are: 2 pure alpha emitters ThA (Po^{216}), ThC^1 (Po^{212}) and 1 pure beta emitter $MsTh_1$ (Ra^{228}).

The amount of the daughter elements Ra^{228}, Ra^{224}, and Pb^{212} in the injectable colloid of the thorium dioxide varies with the method of manufactural purification of the ore. The chemical process removes the daughter product Ra^{228}. Equally important is the varying time lapse between the actual preparation of the colloid and its administration because some daughter elements are absorbed in the wall of the container.[33,48] In the tissue samples (*in vitro*) Th, ThA and ThC reach equilibrium with ThX in 3 days and with RdTh in 1 month.[48]

The daughter elements differ chemically from the parent thorium and are excreted from the body during the first few months, during which time there is also a decrease in the expected amount of total radiation to the body. Rundo[51] found that the alpha emission in the tissues 13 to 14 years after the administration of thorotrast is only one-half of the amount of emission obtained from the same thorotrast when kept *in vitro*. After death, the amount of radioactivity in the tissues increases as no physiologic elimination occurs. This indicates that *in vivo* the isotopes are not in equilibrium.[33] All this makes the calculation of the absorbed dose in the tissues difficult and accounts for the variable figures reported by different investigators. Many methods have been used to determine the total absorbed dose in the body and organs, such as alpha track measurements in the tissue autographs,[46,47] external gamma ray counting[53] densitometry,[52] etc. Morgan *et al.*[33] calculated the dose to the organs from 75 cc. of thorotrast by using alpha tract measurements which were developed by Rotblat and Ward.[47] They found a maximal dose of 8.3 rads a week to the liver and 12.4 rads to the spleen. This, with a RBE of 10 for alpha particles, will give to the liver a dose of 4,300 rems a year, which is a huge dose of

TABLE I

DECAY OF THORIUM^{232}*

Isotope	Synonym	Physical Half Life	Emission			Remarks	Gamma radiation† r/hr. at 1 cm. per mc
			Alpha mev.	Beta mev.	Gamma mev.		
Th^{232}		1.4×10^{10} yr.	4.01 3.95		.059	spontaneous fission	
Ra^{228}	$MsTh_1$	6.7 yr.		.055			
Ac^{228}	$MsTh_2$	6.13 hr.		1.11 .45–2.18	.057 .10 .91 .08–1.64		5.2
Th^{228}	RdTh	1.91 yr.	(83%)† (17%)† 5.42 5.34		.08 .21 .14 .17		0.1
Ra^{224}	ThX	3.64 da.	5.68 5.44		.24		0.06
Rn^{220}	Tn	56 sec.	6.28 6.74		.54		
Po^{216}	ThA	0.16 sec.	6.78				
Pb^{212}	ThB	10.64 hr.		.34 .58	.239 .30 .11–.41		1.3
Bi^{212}	ThC	60.6 min.	6.05 6.09 9.5–10.5	2.25	.040–2.20	34% decays by alpha, 66% by beta emission	2.6
Po^{212}	ThC^1	0.30 μsec.	8.78				
Tl^{208}	ThC^{11}	3.1 min.		1.80 1.0–2.38	2.61 .58 .51 .04–1.09		5.6
Pb^{208}	ThD	stable					

* Compiled from the data given in "The Chart of Nuclids" Dec., 1961, 6th ed. "General Electric Co." Knolls Atomic Power Lab., D. T. Goldman and J. R. Stehn.

† By J. Rundo.[51]

radiation when considering the life long radiation. Rundo[51] found that 47 to 49 per cent of the alpha emitters and 42 per cent of the beta emitters were retained in the spleen. Looney[25] showed, in his comprehensive study on the subject of thorotrast, that the average radiation dose to the liver by one or by combination of different methods (including autoradiography, spectrometry, spectrochemical analysis and excretion studies) varies from about 1 to 9 rads a week when the usual hepatosplenography dose of 75 cc. of 20 per cent thorotrast is used. The most reasonable estimate for the average weekly dose, according to Looney, is 1.5 rads to the liver, 2.5 rads to the spleen and 0.3 rads to the bone marrow.

Case II received 100 cc. of 20 per cent thorotrast 33 years prior to his death. When using the above recommended figure of 1.5 rads per week for 75 cc. thorotrast, we found that the patient's liver received a total dose of 3,400 rads during his lifetime. This is a huge dose of 34,000 rems.

ROENTGENOGRAPHIC DIAGNOSIS

After the intravascular administration of thorotrast, an early homogeneous opacity appears in the liver and spleen as the Kupffer cells in the liver and the sinosidal cells in the spleen phagocytize this colloid. The best way to evaluate the liver with this method is by planigraphy which should be done about 48 hours later.[58] As time goes by, aggregates of thorotrast form in the liver and spleen which give to these organs a lacy, reticulated appearance (Fig. 5). Later, there is a drainage of thorotrast into the regional lymph nodes, especially into the celiac lymph nodes which become very densely opacified (Fig. 5 and 7). The other organs, such as the pancreas, kidneys and lungs, do not show any roentgenographically useful opacifications because the

harbored amount of thorotrast is minute. Looney[25] observed occasional increased thickness in the tibiae and femora but considered it to have equivocal value only. Those who are not familiar with the above described classic appearance of a thorotrast liver may mistakenly interpret the condition as liver calcification. It has been called, for instance, an unusual type of calcification in a cirrhotic liver.[30,62] The increased opacity of the liver in hemochromatosis has a very fine texture, making it sometimes hardly noticeable. This appearance should be kept in mind in the differential diagnosis of early thorotrast hepatolienograms which also show a uniformly fine opacification of these organs. Calcified granulomata, hemangiomata and adenocarcinomatous metastases in the liver do not have the distinctive reticulated lacy appearance of the advanced thorotrast liver. Further supportive findings which indicate the latter are the associated small opacified spleen and very dense regional lymph nodes.

At present, colloidal thorium dioxide is used only in patients who have a disease, such as disseminated carcinomatosis, in which life expectancy is very limited and where there is also a need to observe the action of chemotherapeutic agents on liver metastases. In the latter case Talley *et al.*[58] give 50 cc. of thorotrast intravenously and take planigrams of the liver approximately 48 hours later. While using this material, one should also be aware of possible hypersensitivity phenomena, "colloid reaction," persistent vomiting, and bleeding tendency.[8,11,43,58]

SUMMARY

Two cases of severe thorotrast reaction are reported. In 1, a 60 year old male, extravasation of thorotrast had occurred into the carotid sheath 27 years previously at attempted carotid arteriography which resulted in obliteration of the right common carotid artery and internal jugular vein. The second case, a 53 year old male, developed a liver cell type of carcinoma (hepatoma) 33 years after the intravenous administration of thorotrast.

In the literature we found 65 cases of liver malignancies (including our Case 11) which were reported in association with previous intravascular administration of thorotrast. Of this number, the majority (41) were sarcomas, principally hemangioendotheliomas. There were 24 carcinomas of which 8 were hepatomas, including our Case 11, and 11 cholangiomas; 5 were not classified.[3]

The history, dosage, roentgenographic diagnosis, sequelae, and the present day use of this colloidal form of thorium dioxide are discussed.

Another factor in liver carcinogenesis was present in Case 11; namely, chronic alcoholism. The high relationship of liver cell carcinomas with Laennec's cirrhosis is well accepted. However, one cannot state with certainty that in this case, the chronic use of alcohol added any additional cirrhotic changes to the already present severe cirrhosis due to alpha rays. The principal carcinogenic effect in this case is considered to be the extremely high absorbed dose of radiation; namely, 34,000 rems to the liver from the alpha particles.

In Case 1, the severe granulomatous desmoplastic reaction from this long term alpha emitter did cause a complete obliteration of the right common carotid artery and of the internal jugular vein. There was also an associated right sided vocal cord paralysis, Horner's syndrome, and paresis of the ninth to twelfth cranial nerves.

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AN ISODOSE PLOTTER USING MODIFIED ISOTOPE INSTRUMENTS

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VARIOUS techniques have been used to obtain isodose contours by photographic film densitometry.[1,3,4] The method described here uses an electro-mechanical device to scan the film and print isodensity contours. Figure 1 shows the assembled system.

The basic components of the system are shown in Figure 2. The unit, referred to as the light chopper, contains a tungsten lamp, lens, and motor-driven chopper wheel. It produces a light beam pulsed 60 times a second. This beam passes through the film being scanned and impinges upon the cathode of the phototube. A collimator on the light chopper housing limits the diameter of the light spot at the surface of the film to 3 mm. Electrical pulses, produced in the anode circuit of the phototube as a result of the transmitted light, are then fed to the pulse-height analyzer. Those pulses accepted by the analyzer are then fed into a binary scaler which in turn drives the printer. Since the amplitude of the pulses is related to the film density, it is only necessary to select pulses of a particular amplitude in order to record a specific density. The analyzer can be adjusted to select pulses, and hence, densities, of a given value and reject those with a higher or lower value. Figure 3*A* shows a photographic film that was sandwiched in a homogeneous phantom and exposed to a gamma beam moving over an arc of 70 degrees. The resulting density distribution, shown in Figure 3*B*, was used to evaluate a four arc technique for parametrial irradiation. The shape of the isodensity contours indicates the difficulty involved in obtaining the density distribution by conventional methods.[2]

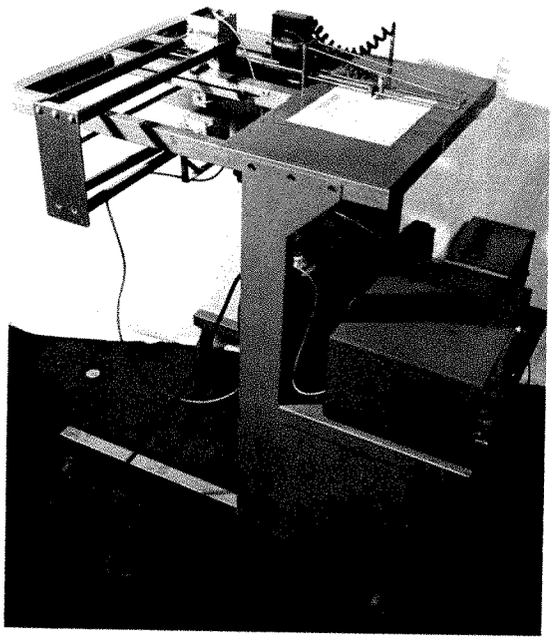


FIG. 1. Assembled system.

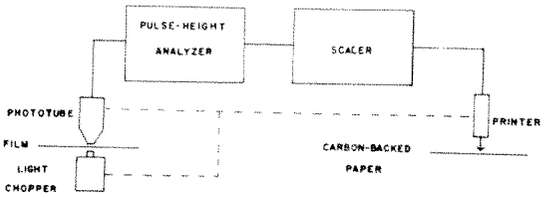


FIG. 2. Block diagram of system.

Approximately 1 minute is required to scan 10 square centimeters of film with this system. One isodensity contour is plotted at a time since a single channel analyzer is used. Different colors of "carbon" paper can be used for each selected density so as to avoid possible confusion in interpreting the scan.

Density variations less than ± 0.025 density units about the selected value will also be recorded due to the inherent resolution of the instrument. This accounts for the spread in the contours shown in Figure 3*B*.

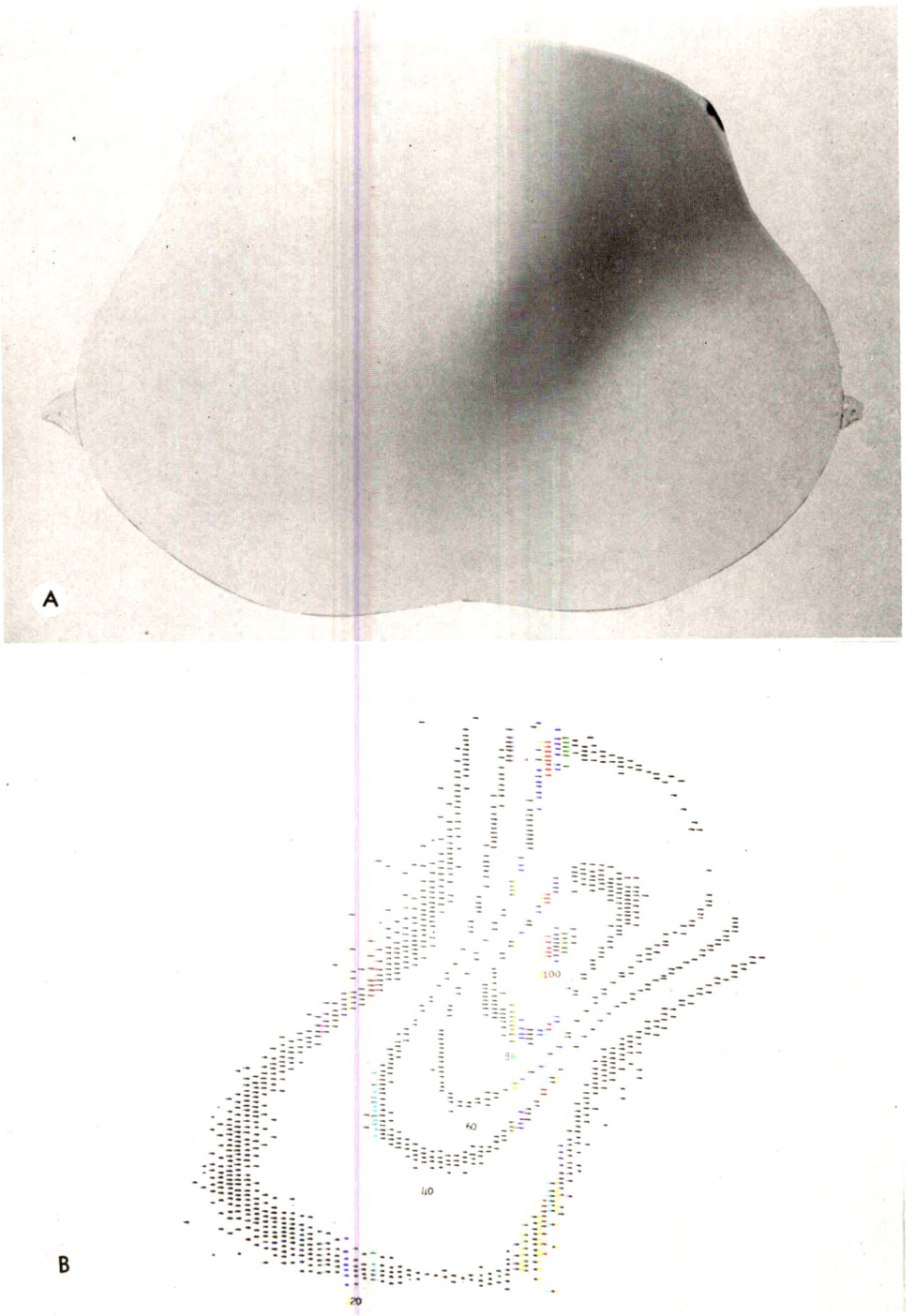


Fig. 3. (*A*) Film exposed to cobalt 60 radiation. (One arc of a "four" arc technique.) (*B*) Corresponding isodensity contours of film in *A*.

In order to modify the original isotope scanner for this application, several components were built and attached to the scanner. These include a light chopper, a phototube housing, and the associated U-shaped supporting arm. A frame for supporting the film was also constructed and mounted on the scanner.

The time constants of the pulse-height analyzer were changed so that it could accommodate the type of electrical pulses involved here. These pulses have a much longer rise time and a greater pulse width than those of a scintillation counter for which the pulse-height analyzer was designed. The printer is driven by the pulse which normally actuates the scaler's mechanical register. The scaler also permits scaling down the tapping rate of the printer to a value low enough for dependable operation.

The advantage of the isodose plotter is realized when complex isodose distributions are to be determined. In such instances, point by point density measurements by conventional methods and manual data plotting would consume considerable time and effort.

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A TECHNIQUE IN TESTING RADIUM SOURCES FOR LEAKAGE*

By JAMES S. BENSON *and* RICHARD H. FETZ†

SEALED sources of radioactive material, including those that are used in medicine, are subject to possible leakage, which may create a significant health hazard. To identify leaking sources, the International Commission on Radiological Protection (ICRP) recommends periodic leak testing of all sealed sources of radioactive materials, including radium.[5] Once found, a faulty source should be disposed of or re-encapsulated.

Radium is encapsulated as a powdered salt which if released could be easily spread over wide areas. For example, one ruptured source could contaminate an entire hospital, necessitating decontamination because of the high radiotoxicity of radium.[2] Clean-up operations for such an incident would be difficult, and the resulting costs could be prohibitive. Through periodic leak testing of radium sources and the disposal of leaking sources, the probability of widespread contamination can be reduced.

Leakage of radium salts and/or radon 222, the chemically inert gaseous daughter of radium, may result from damaged or defective sources. Although radon is less hazardous biologically than radium, radon leakage is an indication of poor source integrity and may be a warning signal for the more serious leakage of the radium salts. Therefore, a radium leak test method should be sensitive enough to detect radon leakage.

In an effort to find a suitable means for leak testing sources on location during a statewide survey of radium users in Georgia, the authors selected from the literature the electrostatic, charcoal-water, and cotton plug methods for experimentation.[3,4,6] The electrostatic and charcoal-water methods required too much time for loading the sources into and removing them from the leak test apparatus. This source handling problem would tend to increase the exposure to the person performing the leak test. The problem would be accentuated when many facilities with large radium inventories were surveyed, and all the radium at each facility was leak tested. Although the cotton-plug method required less handling time, problems of reproducibility were encountered. It was obvious that a method that would allow rapid source handling, while not sacrificing reproducibility and sensitivity, was needed.

METHOD

A method that met these criteria was developed. It is based on the assumption that when a leaking radium source is placed in a sealed container, the gaseous radon leaking from the source will diffuse throughout the volume of the container, and the particulate daughter products of radon will deposit on all surfaces (an observation first made by Madame Curie[1]). Then, a measurement of the activity on the inner surface of the container lid, an area of standard size that allows a constant counting geometry, will give a quantitative reproducible measurement of radon leakage.

The length of time the sources are in the container affects the amount of activity collected because of radon growth. For example, if leakage is constant, a collection time of 1 hour permits the radon to build up to 0.75 per cent of its equilibrium activity, 4 hours to 3.0 per cent, 8 hours to 5.9 per cent, 24 hours to 17 per cent, 48 hours to 30 per cent, and 30 days to 100 per cent. Field tests show that a 24 hour collection time will provide sufficient sensitivity with minimum inconvenience.

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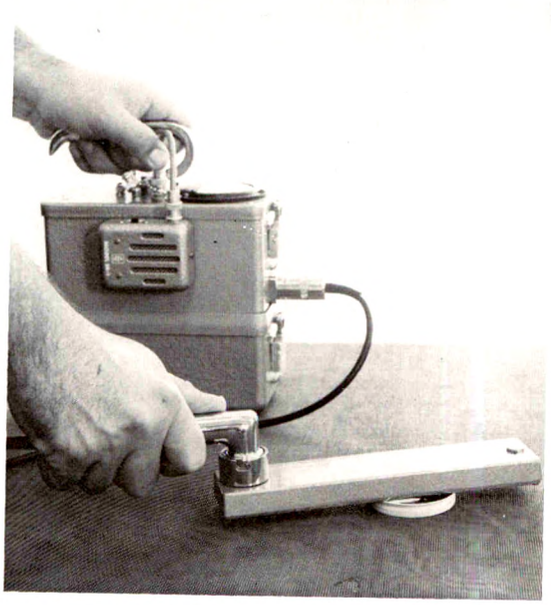


FIG. 1. Checking for alpha activity on jar lid.

After the 24 hour collection time, the container lid is removed, and the probe of an alpha detection instrument is immediately placed over its inside surface (Fig. 1). Although other instruments may be used, alpha instruments offer greater alpha sensitivity and are less sensitive to surrounding gamma fields. Radon daughter activity on the lid indicates radon leakage from either inside the source or from radium salt contamination on the source. It is important that the reading be taken immediately after removal of the lid because the radon daughter activity decays with approximately a 30 minute half life.

Various types of containers such as Petri dishes and metal ointment cans were evaluated as leak test containers. An ordinary glass jar with a rubber gasket seal on the lid to prevent the escape of radon from the container produced the best results. The inner dimensions of the jar used were $2\frac{1}{8}$ inches in diameter, $1\frac{1}{8}$ inches in height, and $\frac{3}{8}$ inch recess on the lid. These dimensions made it possible to place sources of various sizes and shapes in the jar.

As a theoretic illustration of the sensitivity of this system, assume that 0.001 μc of unsealed radium 226 is placed in a jar as described. After 24 hours, approximately 175 disintegrations per minute alpha activity from radon daughter products would be present on the jar lid under the following conditions: (a) 100 per cent of the radon were released by the source, and (b) 100 per cent of the radon daughter products were uniformly deposited on the inner surfaces of the jar.

The use of beaker tongs to handle the jars and 6 inch forceps to handle the radium sources enables the tester to perform the leak test with minimum exposure to the hands (Fig. 2). The use of lead bricks, lead blocks, and lead safes for shielding will reduce gamma exposure to personnel during leak test periods.

CONCLUSION

The jar method was used to leak test radium sources in 21 hospitals in Georgia. A total of 3,388 milligrams of radium contained in 725 sources was leak tested over a 9 month period. Of the 21 hospitals visited, 10 had sources indicating leakage. No exposure higher than 30 mr per month

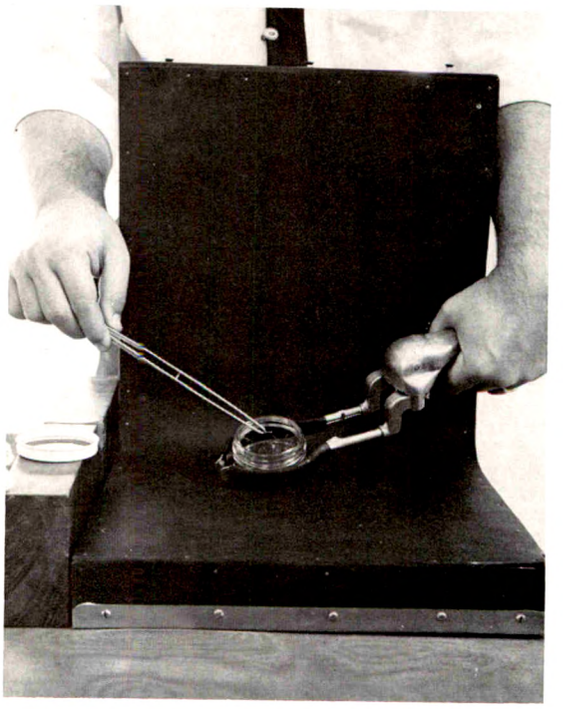


FIG. 2. Placing radium sources in jar.

was indicated by the wrist and waist film badges worn by surveyors during the testing period.

The Georgia Department of Health is continuing the use of the jar method, and it is now being used by personnel in several other State health departments.

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THE RESPONSE OF THE GILL EPITHELIUM OF THE ADULT AXOLOTL (*SIREDON MEXICANUM*) TO ROENTGEN RADIATION*

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CHANGES in the skin epithelium are very important in evaluating the effects of radiation.[7,13,15] Specialized types of epithelium, such as corneal or olfactory epithelium,[10, 14, 16, 18] are usually different from skin epithelium in their respective sensitivities to radiation. Furthermore, there are considerable differences between adult and young animals in the sensitivities of the specialized types of epithelium. In axolotls, for example, the olfactory epithelium is far less radiosensitive in adults than in young animals, being more radiosensitive than corneal epithelium in young animals, but less radiosensitive than corneal epithelium in adults.

The present study deals with the response of still another specialized type of epithelium to radiation, the epithelium of the gills.

MATERIALS AND METHODS

The investigation utilized 40 adult axolotls (*Siredon mexicanum*), 5 to 6 years old. The right gills of each animal were irradiated locally with 2,000 r in 10 animals, with 4,000 r in another 10, and with 8,000 r in a third 10; 10 animals served as untreated controls. Irradiation conditions were as follows: 100 kv., 5 ma., 0.25 mm. Al filter, beryllium window tube; half-value layer, 0.55 mm. Al; intensity, 299.5 r/min.; target-to-object distance, 15 cm. During irradiation, the animals were kept in water in a plastic container 24×32×7 cm.; they were not anesthetized, but were kept under restraint by means of elastic bandages. Body areas not to be irradiated were shielded with a lead covering made from a sheet of lead 4 mm. thick, containing a localizer 22×73 mm.[5] The animals were irradiated only 2 at a time.

For histologic studies, animals were sacrificed, and the gills were fixed in Stieve's acetic acid solution of mercuric chloride and formaldehyde.[28] After decalcification with 0.5 per cent HCl in 80 per cent alcohol, specimens were embedded in paraffin containing 5 per cent beeswax, and were sectioned at 8 μ. The sections were stained with Ehrlich's hematoxylin and eosin, and photomicrographs were made under small (× 40), medium (× 170), and large (× 570) magnifications.

RESULTS

NORMAL GILLS IN ADULT AXOLOTLS

The structure of the gills in adult axolotls is characterized by great variability. This variability is, to some extent, connected with the aging process. The gills of most old animals are very much reduced. Not only are the gill filaments reduced, sometimes even to nonexistence, but also the main trunk of the gills is greatly reduced. In certain old animals, however, the gills are not reduced, and the gill filaments are normal.

Typical of the normal development of the gills in the adult axolotl is the presence of very long and thin gill filaments. The stratified epithelium of the gill trunk is transformed into the simple squamous epithelium of the gill filaments (Plate 1, *A*, *B* and *C*). Normally developed gill filaments are characterized not only by simple squamous epithelium, but also by very large blood vessels, which sometimes occupy essentially the entire volume of the gill filaments, and usually by limited development of pigment

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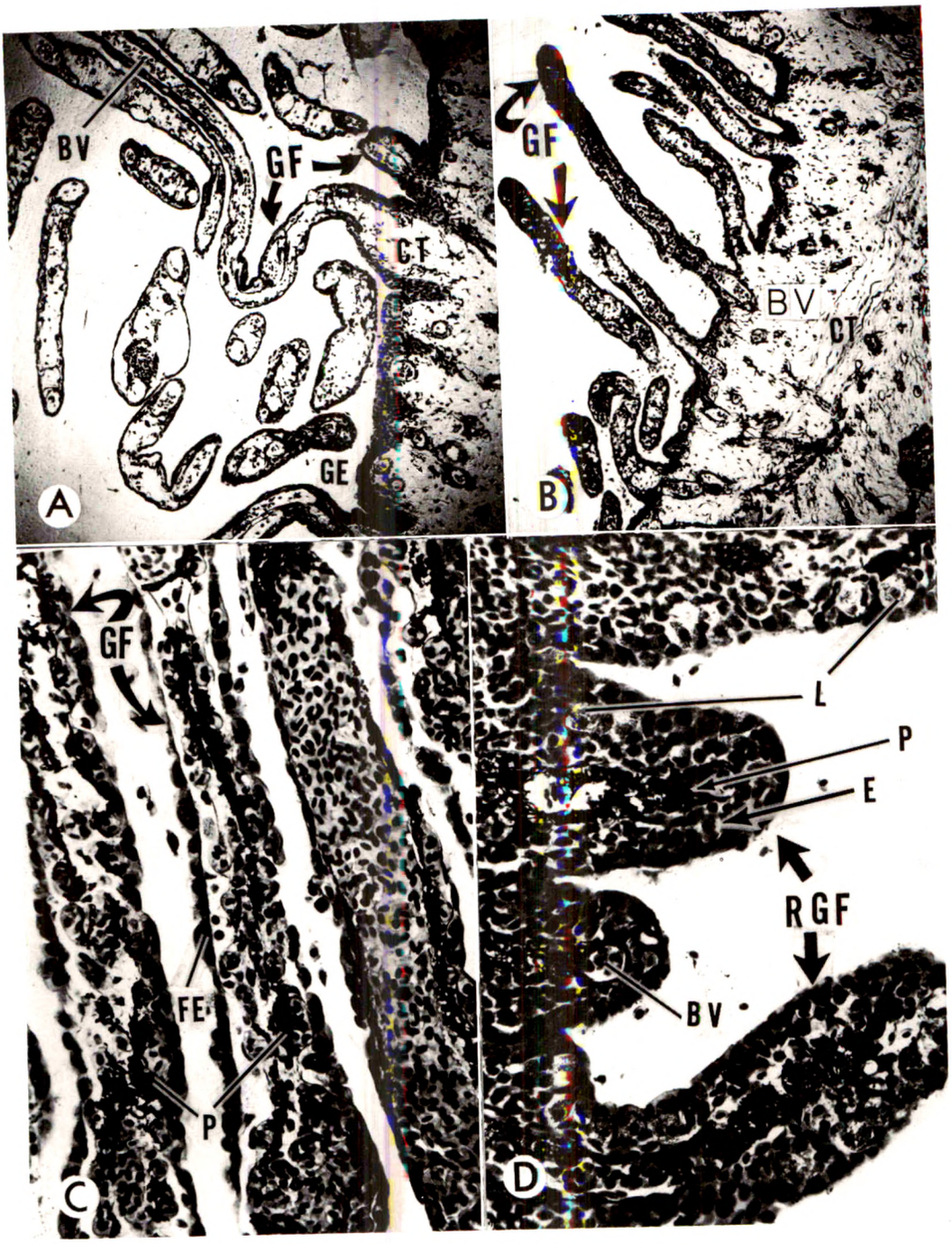


PLATE 1

The normal gills of normal adult axolotls (control animals) and the unirradiated gills (control gills) of experimental animals.

(*A*) Part of a frontal section through the normal gills of a control animal. BV, blood vessel; CT, connective tissue; GE, gill epithelium; GF, gill filament. Photomicrograph, ×40.

(*B*) Part of a frontal section through the unirradiated gills of an experimental animal. BV, blood vessel; CT, connective tissue; GF, gill filament. Photomicrograph, ×40.

(*C*) Part of a frontal section through the unirradiated gills of an experimental animal with normal development of the gill filament (GF). BV, blood vessel; FE, filament epithelium; P, pigment cells. Photomicrograph, ×170.

(*D*) Part of a frontal section through the unirradiated gills of an experimental animal with a reduced gill filament (RGF). BV, blood vessel; E, epithelium; L, Leydig cells; P, pigment cells. Photomicrograph, ×270.



PLATE 2

The irradiated and control gills of experimental animals.

(*A*) Part of a frontal section through the unirradiated gills of an experimental animal with normal development of the gill filament (GL). BV, blood vessel; E, gill epithelium; P, pigment cells. Photomicrograph, ×170.

cells (Plate 1*C*). In the normal development of the gill filaments, the squamous epithelium is typically so thin as to be translucent, and hence the gill filaments are pink in color.

As has been mentioned, the gill filaments of old axolotls may be either normal or more or less reduced. Reduced filaments are comparatively very short and much thicker than normal filaments. They are covered with stratified epithelium, and sometimes this epithelium contains isolated Leydig cells. Relatively small blood vessels and a large accumulation of pigment cells are also characteristic (Plate 1*D*).

The experimental animals' left gills, which were not irradiated, were normal and not distinguishable from the normal gills of control animals (Plate 1*B*; and Plate 2*A*). Reduced filaments were present in the left gills of some experimental animals, but the nature of the reduction involved was such as to make it clear that the process was the same as that observed in control animals, and hence independent of irradiation.

IRRADIATED GILLS IN ADULT AXOLOTLS

Disappearance of the gill filaments may or may not take place in normal development, especially in old axolotls; but it is the rule after irradiation. In the present study, normal filaments were never seen after irradiation. The reduction of irradiated gills is visible in photographs of the heads of experimental animals (Plate 3*C*; and Plate 5*D*).

A reduced filament 78 days following irradiation with 4,000 r (Plate 2*B*) was very short and thick. It was covered with stratified epithelium and had a large accumulation of pigment. The blood vessels typical of normal filaments were absent from the reduced filament. Very limited supplies of blood vessels following irradiation of the gills were also observed in many other instances (Plate 2, *C*, *D* and *E*).

Early fixations demonstrated that major changes in the gill epithelium occur early, even after irradiation with only 2,000 r, the smallest dose used in the present study. Comparison of early and late photomicrographs (Plate 3, *A* and *B*) shows how extensive the radiation effect can be. Although both photomicrographs were taken at the same magnification, the first animal (Plate 3*A*) was fixed 21 days after irradiation with 4,000 r, but the second (Plate 3*B*) was fixed 78 days after irradiation with the same dose. The difference is very great. In the first case, the epithelium is 4 to 5 times as thick, and the cells are larger and very loosely connected, with many cracks, intercellular spaces, and isolated Leydig cells. Large vacuoles in the cytoplasm of the cells are also visible (Plate 3*A*). In the second case, the filament is reduced and atypical, very short and thick, and covered with the stratified epithelium that is characteristic of the gill trunk but not of the gill filament. This epithelium, although abnormal in location, is otherwise completely normal (Plate 3*B*).

Gill epithelium of abnormal thickness can be even thicker 14 days after irradiation with 2,000 r (Plate 3*D*). Typical in instances like this is the formation of large

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(*B*) Part of a frontal section through the gills of an animal 78 days after irradiation with 4,000 r. The filament is undergoing reduction. CT, connective tissue; P, pigment cells. Photomicrograph, ×170.

(*C*) Part of a frontal section through the gills of an animal 64 days after irradiation with 2,000 r. The filament has completely disappeared. BV, blood vessel; CT, connective tissue; E, gill epithelium; P, pigment cells. Photomicrograph, ×40.

(*D*) Part of a frontal section through the gills of an animal 70 days after irradiation with 4,000 r. The filaments are reduced. BV, blood vessel; CT, connective tissue; E, gill epithelium; P, pigment cells. Photomicrograph, ×40.

(*E*) Part of a frontal section through the gills of an animal 100 days after irradiation with 4,000 r. The filaments are reduced. E, gill epithelium; M, muscle; P, pigment cells. Photomicrograph, ×40.

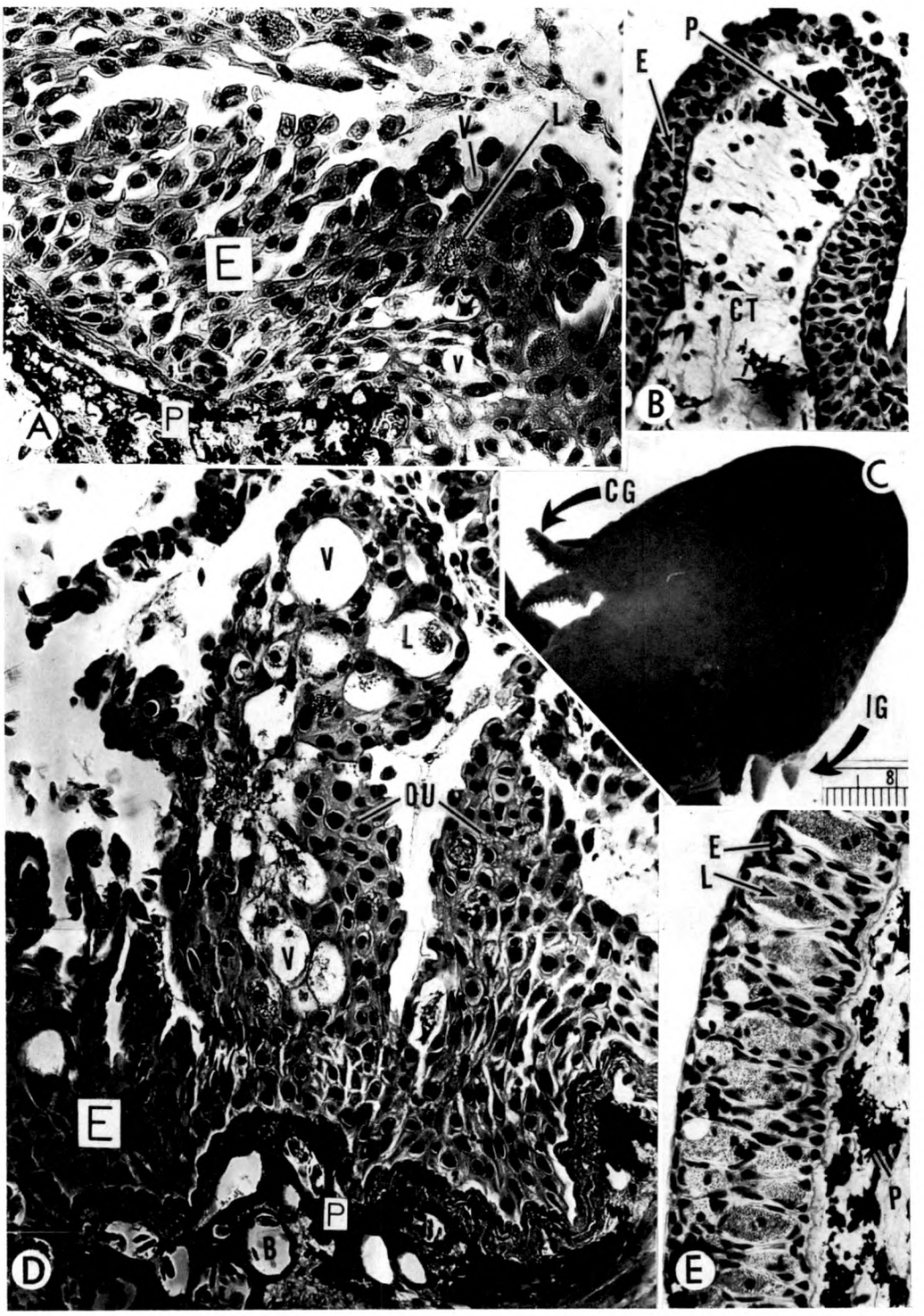


PLATE 3

The irradiated gills of experimental animals.

(*A*) Part of a section through the gill epithelium of an animal 21 days after irradiation with 4,000 r. E, abnormal gill epithelium; L, Leydig cells; P, pigment cells; V, vacuoles. Photomicrograph, ×170.

abnormal outgrowths, which are 9 to 10 times as long as the thickness of the epithelium in the animal fixed 78 days after irradiation (Plate 3*B*). Large cells, large and giant vacuoles in the cytoplasm, loose connection between the cells, and isolated Leydig cells were also observed. It is evident that the gill epithelium became completely disorganized very soon after irradiation. Gradually, external cells and cell complexes separated completely, and all irradiated epithelium disappeared, together with the gill filaments. Later the gill epithelium would be replaced with typical skin epithelium containing many Leydig cells, as is evident in an animal fixed a year after irradiation (Plate 3*E*).

Disappearance of the gill filaments proceeded at different rates in different cases. In some cases, the filaments completely disappeared within 64 days after irradiation (Plate 2*C*); in other cases, remnants of the filaments still existed 70 to 100 days after irradiation (Plate 2, *D* and *E*).

Changes in some details of the gill epithelium were visible 21 days after irradiation with 4,000 r (Plate 4, *A*, *B* and *C*). Multiple small vacuoles or single large ones often developed in the cytoplasm of epithelial cells (Plate 4*A*), and the connections between epithelial cells often became loose (Plate 4, *B* and *C*). Pigment cells accumulated to a much greater extent in irradiated gills than in control gills (Plate 4, *D*, *E* and *F*).

Special attention should be given to the response of the gill epithelium to irradiation with 8,000 r. In the present study, 8,000 r was the lowest dose that induced the development of giant cells. The presence of giant cells is highly characteristic of radiation damage in general, but they were not observed in the gill epithelium after irradiation with only 2,000 or 4,000 r. Several photomicrographs at different magnifications show changes in details of the gill tissues after irradiation with 8,000 r (Plate 5, *A*, *B*, *C* and *E*; and Plate 6, *A*–*F*). Comparison of *A* in Plates 4 and 5 clearly demonstrates the difference in the sizes of cells. Like giant cells, giant nuclei were observed only after irradiation with 8,000 r. Some of the giant cells were multinucleated (Plate 5*A*; and Plate 6*E*); some had small or large vacuoles (Plate 5, *B* and *E*).

Between the enlarged or giant cells, it was possible to find portions of epithelium almost normal in appearance, with cells of normal size (Plate 5*C*). Connections between epithelial cells were loose in many instances. In some places, there were large accumulations of pigment cells (Plate 5*C*). Especially interesting is the presence of mitotic figures in epithelial cells in close proximity to giant-cell epithelium. In one instance, three mitoses were very near to one another and to giant cells (Plate 6, *A* and *C*).

DISCUSSION

The fact that giant cells were observed only following irradiation with 8,000 r is not difficult to explain. After irradiation, the gill epithelium is generally destroyed, and with it, of course, any gill epithelium cells that might have become giant cells.

(*B*) Part of a section through the gills of an animal 78 days after irradiation with 4,000 r. CT, connective tissue; E, gill epithelium, normal in appearance; P, pigment cells. Photomicrograph, ×170.

(*C*) Head of experimental animal G-21. (The epithelium of the irradiated gills of this animal is shown in Plate 2 *E*.) CG, control gills (not irradiated); IG, irradiated gills. Photograph.

(*D*) Part of a section through the gill epithelium of an animal 14 days after irradiation with 2,000 r. B, blood vessel; E, abnormal epithelium; L, damaged Leydig cell; OU, abnormal epithelial outgrowth; P, pigment cells; V, vacuoles. Photomicrograph, ×170.

(*E*) Part of a section through the gill epithelium of an animal 429 days after irradiation with 2,000 r. E, epithelial cells; L, Leydig cells; P, pigment cells. Photomicrograph, ×170.

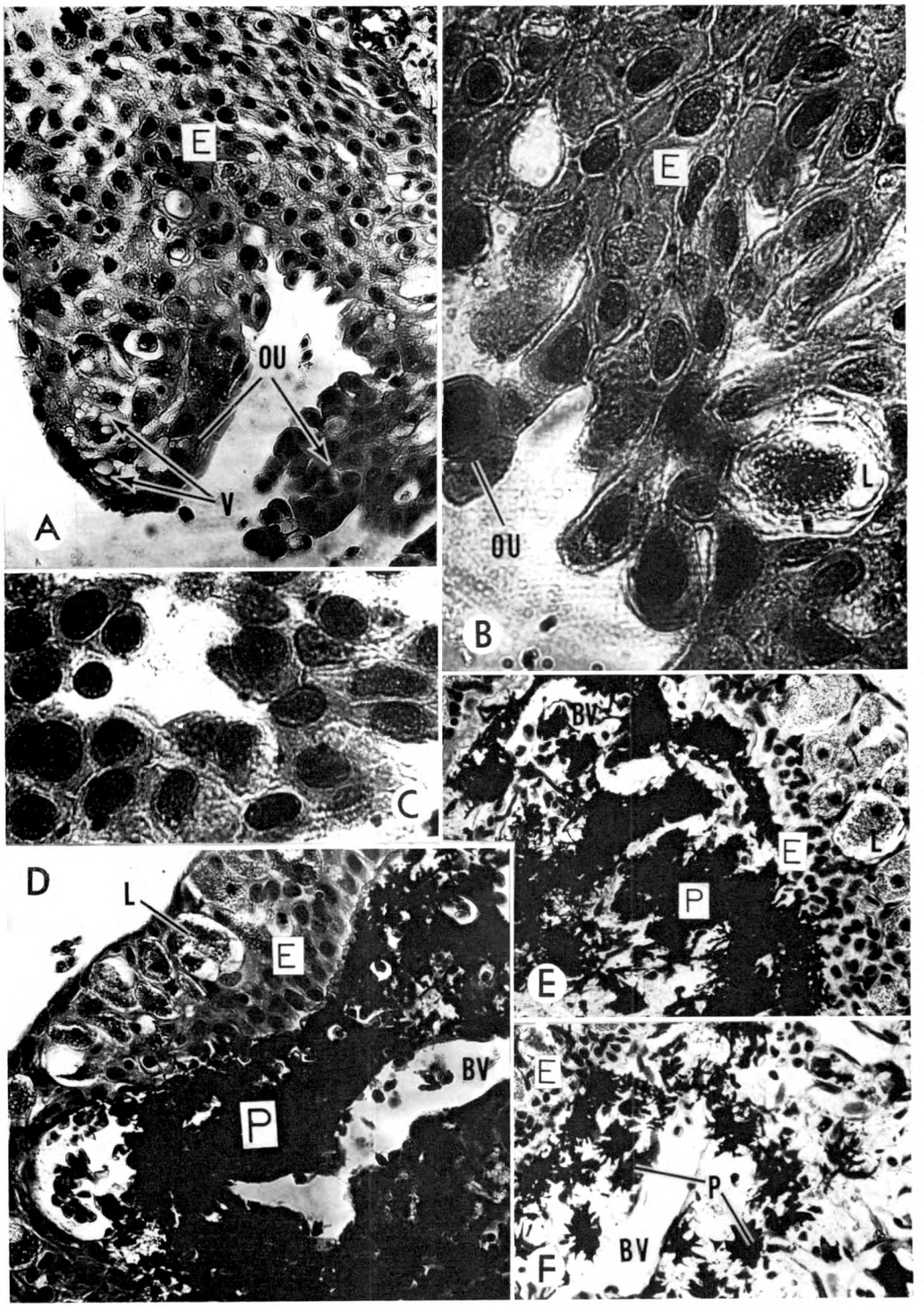


PLATE 4

The tissues of irradiated gills.

(*A*) Part of a section through the gill epithelium of an animal 21 days after irradiation with 4,000 r. E, epithelial cells; OU, epithelial outgrowths; V, vacuoles in epithelial cells. Photomicrograph, ×170.

The destroyed gill epithelium is then replaced with skin epithelium derived from the periphery of the gills. Skin epithelium is far less radiosensitive than gill epithelium, and a relatively small dose of radiation that completely destroys the gill epithelium may leave the surrounding skin epithelium essentially unaffected. After irradiation with a dose as large as 8,000 r, however, even the peripheral skin epithelium is damaged to some extent, and it is this damaged skin epithelium that is the source of any giant cells that are found in the region.

It should be noted that the gill epithelium and gill filaments are destroyed very early, only 14 to 21 days after irradiation, even when the dose is as small as 2,000 r, the smallest used in the present study. After irradiation with 8,000 r, it is very possible that destruction occurs much earlier, perhaps less than 10 days after irradiation. Giant cells, however, are not observed until about 55 days after irradiation. Under the circumstances, the development of giant cells is presumably a manifestation of late damage (secondary damage) to the skin epithelium that replaces the destroyed gill epithelium.

The gill epithelium and gill filaments that were replaced with skin epithelium were completely destroyed after irradiation with 2,000 r, the smallest dose used in the present study. It follows that the gill epithelium is one of the most radiosensitive types of epithelium in the adult axolotl.

In the young axolotl, sensitivity and response to irradiation vary a good deal from one type of epithelium to another (Table 1). The individual types fall into two general groups: first, skin epithelium and related types, such as corneal and olfactory epithelium; and second, the epithelium of internal organs, such as the kidneys, the small intestine, and the cloaca. The types of epithelium in the second group are comparatively radioresistant. In the epithelium of the small intestine, the development of giant cells is not observed, although nuclei are sometimes enlarged. In the kidneys, giant cells are very rare. The cloaca is the most radiosensitive of the internal organs, being intermediate in sensitivity between the other internal organs and the skin. In the cloacal epithelium, giant cells are not infrequent (Table 1).

The skin epithelium of the young axolotl always shows a definite response to radiation (Table 1). Giant cells develop, and some of them have exceptionally large nuclei. The irradiated epithelium gradually degenerates, desquamates, and disappears, and is then replaced with normal skin epithelium from the peripheral region, which has been irradiated only in part, or has not been irradiated at all. It should be noted that giant cells in the skin epithelium are at least 2 or 3 times as large as those in internal organs, and in fact are much more typical of the skin epithelium.

The specialized modifications of skin epithelium, such as corneal and olfactory epithelium, are much more radiosensitive than the skin epithelium in young axolotls (Table 1). The olfactory epithelium is especially sensitive. Only in 17 per cent of all of the

(*B*) Part of a section through the gill epithelium of the same animal as in *A*. E, epithelial cells; L, Leydig cells; OU, epithelial outgrowth. Photomicrograph, ×570.

(*C*) Part of a section through the gill epithelium of an animal 14 days after irradiation with 2,000 r. Photomicrograph, ×570.

(*D*) Part of a section through the gills of an animal 14 days after irradiation with 2,000 r. BV, blood vessels; E, epithelial cells; L, Leydig cell; P, accumulation of pigment cells. Photomicrograph, ×170.

(*E*) Part of a section through the gills of an animal 64 days after irradiation with 2,000 r. BV, blood vessel; E, epithelial cells; L, Leydig cell; P, pigment cells. Photomicrograph, ×170.

(*F*) Part of a frontal section through the unirradiated gills of an experimental animal. BV, blood vessel; E, epithelial cells; P, pigment cells. Photomicrograph, ×170.

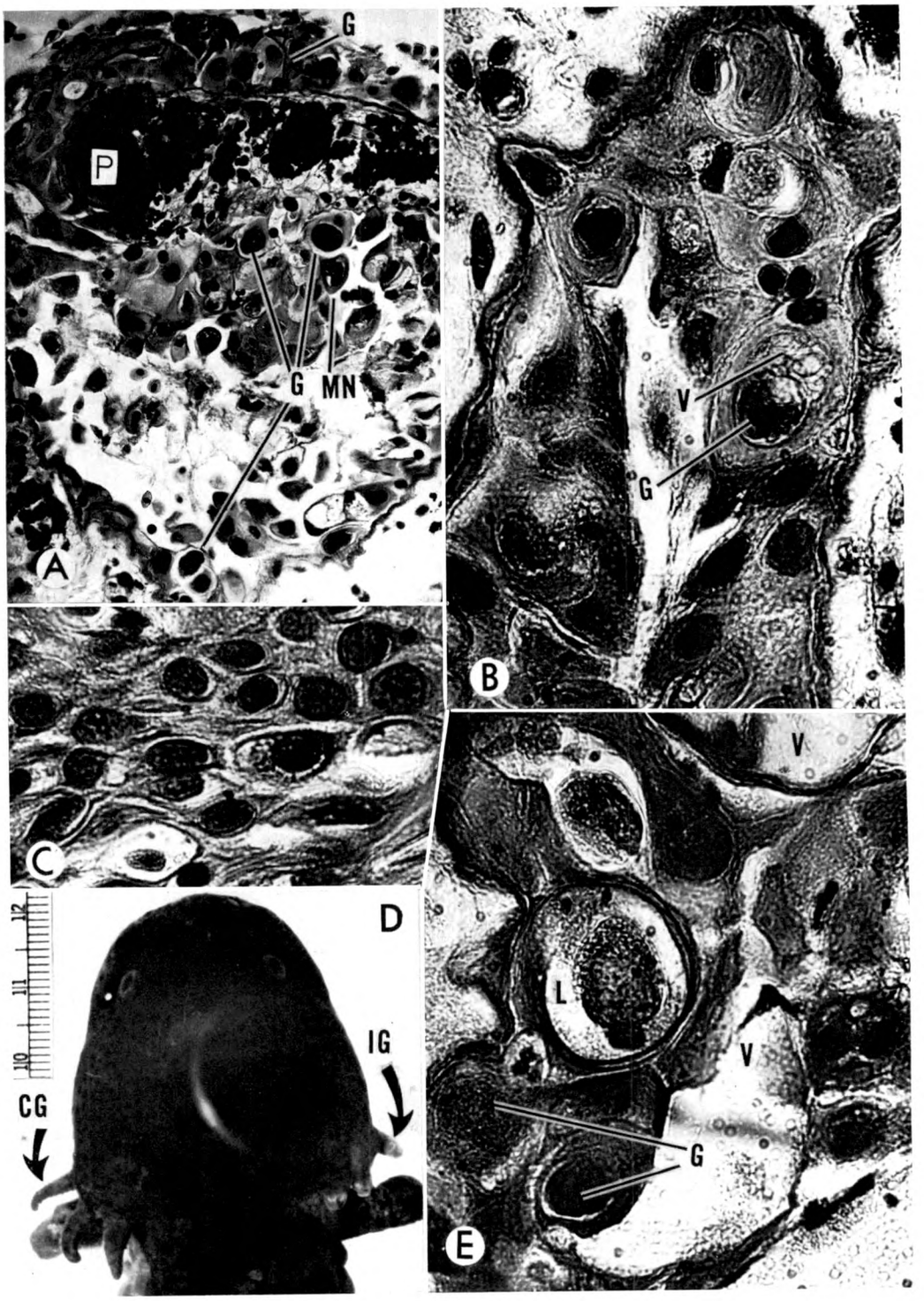


PLATE 5

The head and various portions of the gill tissues of animal G-35, 55 days after irradiation with 8,000 r.

(*A*) Part of a section through the gill epithelium. G, epithelial giant cells; MN, multinucleated epithelial cell; P, accumulation of pigment cells. Photomicrograph, ×170.

(*B* and *E*) Various portions of the gill epithelium, containing giant cells (G). L, Leydig cell; V, vacuoles. Photomicrographs, ×570.

(*C*) Part of a section of gill epithelium containing only cells of normal size. Photomicrograph, ×570.

(*D*) Head of animal. CG, control gills (not irradiated); IG, irradiated gills. Photograph.

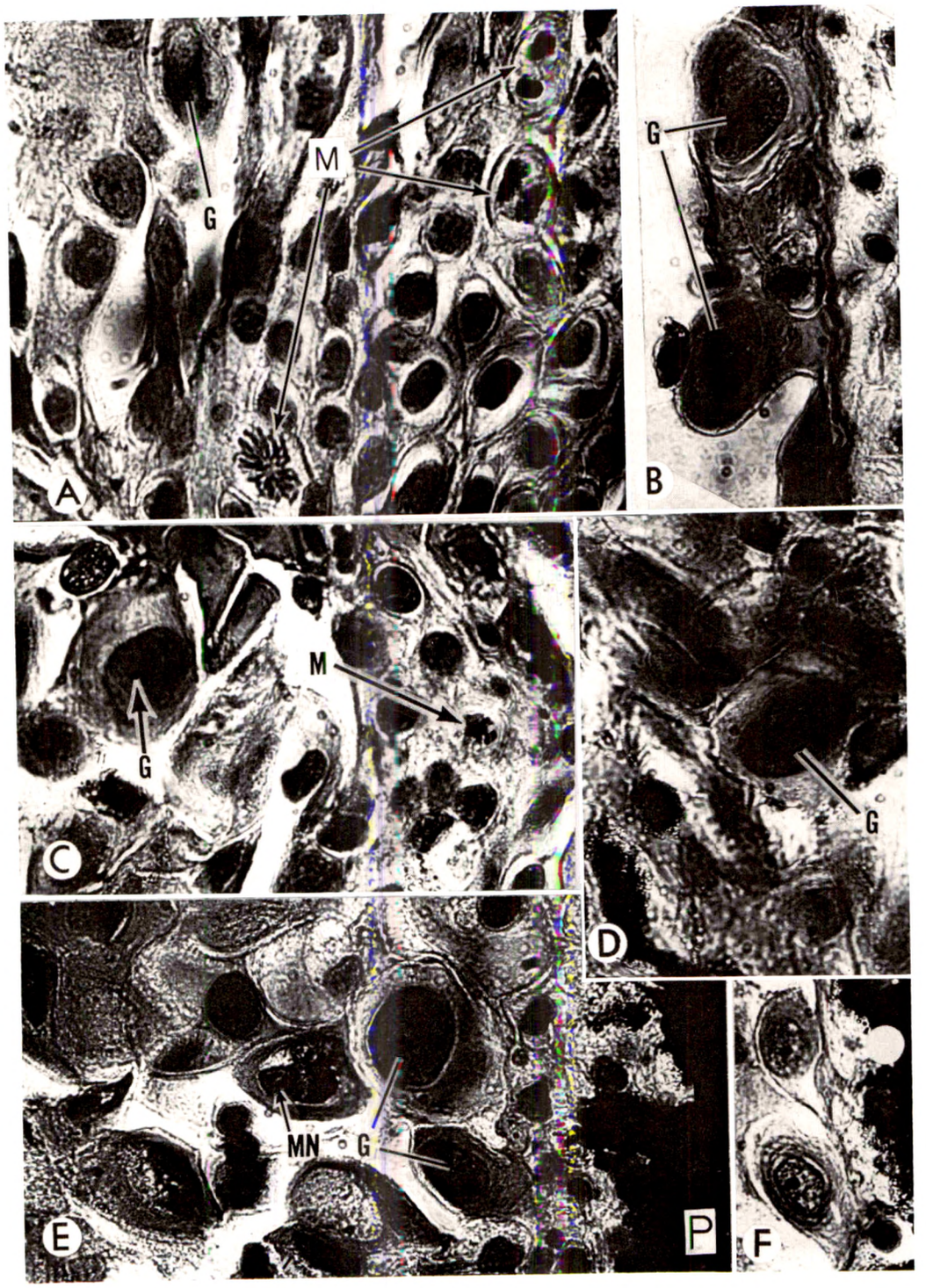


PLATE 6

(*A–F*) Various portions of the gills of animal G-35 (same as in Plate 5) 55 days after irradiation with 8,000 r. All photomicrographs made with the same magnification (×570). G, giant cells; M, mitosis; MN, multinucleated epithelial cell.

TABLE I

RESPONSES OF VARIOUS TYPES OF EPITHELIUM IN YOUNG AXOLOTLS TO ROENTGEN RADIATION

Epithelium of	Age of Animals at Irradiation (days after hatching)	Irradiation		Response (percentage of all irradiated animals clearly exhibiting response)
		Type	Dose (r)	
1. Skin of head[13]	14	local	500–3,000	1. Extremely uneven outer surface. Outgrowths. Many giant cells. Vacuoles in cytoplasm. Desquamation of degenerate epithelium and replacement with normal skin epithelium
2. Skin of lumbosacral region[4]	30	local	750–8,000	2. Development of giant cells. Gradual degeneration and destruction of irradiated epithelium and replacement with normal skin epithelium
3. Skin of tail[3]	5–12	local	2,000–6,000	3. (Same as preceding entry)
4. Skin of various portions of body[7]	30	both*	3,000	4. Damage (85%); severe damage (46%). Development of giant cells. Outside surface of degenerating epithelium uneven. Gradual desquamation and disappearance of giant cells and replacement with normal skin epithelium
5. Cornea[14]	12–14	local	500–9,000	5. Reduction in numbers of cells. Transformation into simple squamous epithelium. Gradual disorganization, desquamation, and replacement with skin epithelium
6. Cornea[8]	25–32	local	3,000	6. Reduction in number of layers of cells. Enlargement of cells. Development of Leydig cells. Damage to cornea (38%). Complete disappearance of cornea, and replacement with skin epithelium (30%)
7. Olfactory chambers[10]	25–32	local	3,000	7. Abnormal distribution of specialized cells (17%). Disappearance of sensitive olfactory buds (54%). Complete disappearance of olfactory epithelium and replacement with skin epithelium (28%)
8. Cloaca[7]	30	both*	3,000	8. Damage (94%); severe damage (35%). Enlargement of cells or development of giant cells. Degeneration
9. Small intestine[7]	30	both*	4,000	9. Damage (75%); severe damage (11%). In most cases, only enlargement of nuclei
10. Kidneys[7]	30	both*	3,000	10. Damage (35%); severe damage (15%). In most cases, only enlargement of nuclei. In some cases, development of giant cells

* Total-body and local irradiation.

animals studied was there no more than slight damage, limited to abnormal distribution of olfactory cells; in 54 per cent, there was severe damage, the sensitive olfactory buds disappearing completely; and in 28 per cent, the olfactory epithelium disappeared completely and was replaced with skin epithelium containing many Leydig cells, which are never present in normal olfactory epithelium.[10]

The responses of the various types of epithelium to radiation are not at all the same in young axolotls as in adult axolotls (Table II). The most typical response of the skin epithelium of young axolotls, the development of giant cells, does not occur after irradiation of adult axolotls except in extremely rare cases, and then only to a limited extent. The giant cells that are observed in the adult animals are never comparable in either size or number to those that are observed in the young animals. As a matter of fact, the present author has observed giant cells in adult axolotls only in two instances. In one, giant cells occurred in the interstitial epithelium of irradiated olfactory chambers.[18] In the other instance, giant cells occurred in the skin epithelium that replaced gill epithelium destroyed after irradiation with 8,000 r, as has been reported in the present paper.

The development of giant cells following

irradiation is most typical of young, actively growing tissues. The voluminous literature concerning this situation has been discussed in detail in previous papers,[13,15] and thus needs attention here only in regard to certain points. Giant cells have been found in all types of irradiated young vertebrates, invertebrates and plants, as well as among microorganisms. Perhaps, however, they are especially typical of fast-growing tumors.

According to Warren,[35] cells and their nuclei gradually enlarge after irradiation, and giant cells with bizarre giant nuclei can be found in irradiated tumors. Whitmore and his associates[37] conclude that giant cells evidently retain considerable metabolic function. After irradiation, cell division is inhibited, but the majority of cells greatly increase in volume. Individual cells with volumes more than 200 times normal have been observed in some cases.[33,34] Brues and Stroud[1] observed the formation of giant nuclei in certain continuously irradiated tumors, including Flexner-Jobling carcinoma and Jensen sarcoma in rats, and sarcoma 180 and Hall mammary carcinoma in mice.

The irradiated cell, says Kaplan,[25] "seems able to do everything but divide, and looks normal enough except for its enormous size, which is a consequence of sustained synthesis of protein and other cell constituents, divorced from the usual partition of these products of growth among a succession of daughter cells." As Lea[26] puts it, "if the cells are prevented from dividing but continue to grow at the normal rate, then the size of the cells will increase instead of the number."

In adult tissues, where mitotic figures are extremely rare, true giant cells are not likely to be found after irradiation. Slight enlargement of cell nuclei, however, is observed in many irradiated tissues.

Total-body irradiation is typically followed by variable damage to the epithelium of the skin. Cell nuclei may enlarge, Leydig cells (glandular cells that are very numerous in normal skin epithelium) may disappear, and the number of cells in general may decrease. In some areas, part of the epithelium may be transformed into homogeneous tissue without cell borders or nuclei. Ulcer formation was observed in 50 per cent of axolotls irradiated with 12,000 r. Near the ulcers, some portions of the epithelium were transformed into homogeneous masses, which possibly represented the initial phase in the formation of roentgen ulcers.[9] In the epithelium of the small intestine, cell nuclei were enlarged, and mucus produced by the glandular cells was not excreted, thus accumulating in greater or lesser amounts.[9]

In adult axolotls, the cornea is more radiosensitive than the skin epithelium.[16] In some cases, cells may appear almost normal; but in other cases, nuclei may be greatly enlarged. After irradiation, the development of pigment cells in the cornea is typical. Destruction of the corneal epithelium is followed by replacement with skin epithelium from the peripheral zone.

The change in the radiosensitivity of the olfactory epithelium with age is remarkable.[18] In young axolotls, the olfactory epithelium is one of the most sensitive types of epithelium; in adults, it is one of the most resistant. Even after irradiation with 10,000 r, the olfactory epithelium is normal in some places. Complete destruction of the olfactory epithelium and replacement with skin epithelium have never been observed. The development of giant cells in the interstitial epithelium of the olfactory chambers is a special case. It is probably an example of roentgen stimulation, which will be discussed later in the present paper.

In one type of epithelium in adult axolotls, the development of giant cells following irradiation would be expected, and does occur. That type of epithelium is the skin epithelium of limb regenerates (Table 11). This exception to the general rule serves to emphasize the correctness of the explanation that has already been given. Regenerating limbs contain very actively growing tissues, much like the tissues of a young animal. Finding giant cells in such

TABLE II

RESPONSES OF VARIOUS TYPES OF EPITHELIUM IN ADULT AXOLOTLS TO ROENTGEN RADIATION

Epithelium of	Irradiation		Response (percentage of all irradiated animals clearly exhibiting response)
	Type	Dose (r)	
1. Skin of limb regenerates[13]	local	4,000 and 6,000	1. Damage (70% at 4,000 r; 100% at 6,000 r). Development of giant-cell degenerating epithelium. After complete disorganization and destruction, replacement with new normal epithelium
2. Skin of various portions of body[9]	total-body	12,000	2. Extensive and highly variable damage (87%). Disappearance of Leydig cells typical. Enlargement of cell nuclei; reduction in number of cells. In some places, formation of homogeneous tissue without cell borders or nuclei
3. Cornea[16]	local	1,000–10,000	3. Great variation in response. Cells almost normal in some cases; extensive enlargement of nuclei in others. Destruction of corneal epithelium and replacement with skin epithelium (80–100%). Presence of pigment cells
4. Olfactory chambers[18]	local	3,000–10,000	4. Damage (90–100%). Even after irradiation with the largest doses, epithelium is normal in some places; disorganization of all layers in others. In some places, interstitial epithelium enlarged or even giant nuclei present
5. Gills*	local	2,000–8,000	5. Destruction of epithelium and complete disappearance of filaments; replacement with skin epithelium containing enlarged and giant cells (100%)
6. Small intestine[9]	total-body	12,000	6. Damage (75%). Enlargement of cell nuclei. Mucus produced by glandular cells not excreted normally, and hence accumulated in greater or lesser amounts

* Present study.

tissues following irradiation is only to be expected.

As has been mentioned, giant cells were observed in the present study. It is important to note, however, that the giant cells were not observed in the irradiated epithelium of the gills, but in the skin epithelium that replaced the destroyed gill epithelium. Such replacement of specialized epithelium with skin epithelium is to some extent comparable with regeneration.

The extreme differences between different types of epithelium and between young and adult animals in sensitivity and response to radiation have already been pointed out. Perhaps the most striking contrast is that shown by the specialized olfactory epithelium of the olfactory chambers. In young axolotls, the olfactory epithelium is one of the most sensitive types of epithelium. In adult axolotls, it is so resistant that 10,000 r is not enough to destroy it. Even 12,000 r produces only slight damage in the highly resistant epithelium of the small intestine. Almost as striking is the contrast between the olfactory epithelium and the tissues of the gills in the adult animals. Despite the extreme resistance of the olfactory epithelium, the gill filament and epithelium are so sensitive that they are completely destroyed in 10 to 15 days after irradiation with only 2,000 r. Such examples make clear how much the different types of a single tissue—epithelium—can vary in their sensitivities and responses to radiation.

The radiosensitivities of melanophores (pigment cells) in young axolotls also vary a good deal from one part of the body to another.[15] The melanophores in the tail appear to be the most sensitive, as they almost disappear after irradiation. Those in the head are highly resistant. Those in the eye are especially resistant, and are the most resistant cells in the eye; they do not decrease in number even during complete degeneration of the irradiated eye. Those in the liver are not only resistant to radiation, but actually undergo large increases in

number after irradiation; in some animals, they accumulate in the liver to such an extent that the entire liver is black, and normal liver cells can be found only in some regions. Finally, radiation can induce the development of melanophores in tissues where they do not ordinarily occur. After irradiation, melanophores can be found in large numbers in the epithelium of the cornea, which ordinarily contains no melanophores whatever.

The presence of mitotic figures in close proximity to damaged epithelium containing enlarged and giant cells, as was observed in the present study, is significant. In the tissues of adult axolotls, mitosis is extremely rare. The unusual number of mitoses concentrated in one place near obvious radiation damage evidently represents an instance of roentgen stimulation.

Radiation stimulation has been discussed many times before,[2–4,6,7,11,13,15,18,19] but it will be necessary to consider it again in the light of new observations and facts. Stimulation of plants and miroorganisms by radiation is a well-established phenomenon supported by many observations.[24,25,29,31] Radiation activates development by accelerating the rate of cell division promoting the accumulation of biomass, and intensifying other physiologic processes.

In the lower vertebrates, and particularly in the axolotl, radiation stimulation has been observed almost exclusively in young animals. This fact must be emphasized. For example, a radiation-induced secondary tail developed after irradiation of axolotl larvae only 10 days after hatching,[19] and additional limbs developed after irradiation of axolotl larvae 24 to 30 days after hatching.[4] Likewise, epithelial outgrowths developed after irradiation of young *Rana catesbiana* tadpoles.[6] In addition, mitosis in the spleen was stimulated after irradiation of axolotl larvae 30 to 47 days after hatching,[7] the corneal epithelium became thicker after irradiation 12 to 14 days after hatching,[14] and peculiar outgrowths formed in the skin epithelium after irradiation 14 days after hatching.[13]

In the adult axolotl, radiation stimulation has been observed only in rare cases. After irradiation of the olfactory chambers, the interstitial epithelium underwent abnormally extensive development;[18] and after irradiation, melanophores and blood vessels developed in the cornea,[16] where such cells and structures are normally absent. In both cases, cells and tissues underwent abnormal development, but mitosis was never observed in the regions involved. It is clear, then, that the radiation-stimulated mitotic activity in the gills of adult axolotls in the present study is the first instance of its kind in adult axolotls.

The mitoses that occurred in this study are superficially comparable to the intense mitotic activity that occurs in the spleens of young axolotls after total-body irradiation with a lethal dose. Even so, the mitotic activity in the spleen of an irradiated animal is only an augmented version of the activity in the spleen of a normal animal, where it is completely usual for many mitotic figures to be observed. In the present study, mitosis was never observed in the gills of a normal adult animal. It is interesting that mitosis was observed in close proximity to damaged cells in both of the animals affected. Similar observations were made in the case of unusual epithelial outgrowths that formed in the irradiated tails of *Rana catesbiana* tadpoles.[6] These outgrowths occurred between portions of degenerating giant-cell epithelium, and were themselves composed of cells of normal size, with many mitotic figures.

All of these observations give a very definite impression that radiation stimulation is the result of some stimulus produced by cells that become damaged or degenerate after irradiation. Probably this stimulation is not caused directly by the action of roentgen rays, but is a secondary stimulation by disintegration products (substances of the type that have been called "necrohormones") formed in the region of damage or degeneration. Such a type of stimulation has been reported by a number of investigators.[21,23,32,38]

Similar observations were made after the irradiation of *Triton cristatus* limbs.[2, 20] Regeneration began after a period of regression, and the authors explained the beginning of new growth as a result of the accumulation of "necrohormones" during the period of regression. The development of abnormally thick epithelium consisting of many layers of cells of normal size was stimulated near necrotic epithelium in tail regenerates in *Pelobates fuscus* tadpoles.[30] According to Czepa,[22] interstitial cell growth following roentgen irradiation is stimulated by a necrohormone formed in partially destroyed tissues of the testis. Weber[36] reported the formation of the same type of substance after the irradiation of plants. In all such cases, it is possible that the stimulatory effect is observed only after the accumulation of a sufficient quantity of disintegration products ("necrohormones" or "wound hormones") resulting from the destruction of irradiated cells.

The development of additional limbs following local roentgen irradiation is paralleled by a similar development of additional limbs, also in the absence of amputation, following the tying of ligatures around the extremities of axolotls, as reported by Nassonov.[27] In the latter case, however, the superregeneration, or growth of supernumerary limbs, occurred in the proximal portion of the extremity. Nassonov concluded that the abnormal stimulation of the regeneration process was due to the formation of disintegration products ("necrohormones"). Presumably, this conclusion is applicable to both types of superregeneration.

SUMMARY

1. The right gills of adult axolotls (*Siredon mexicanum*), 5 to 6 years old, were locally irradiated with 2,000 r in 10 animals, 4,000 r in 10, and 8,000 r in 10; 10 animals served as untreated controls.

2. Disappearance of the gill filaments is possible in the course of normal development, especially in old axolotls, but was the rule after irradiation. In the present study, normal filaments were never seen after irradiation.

3. The gill filament and the gill epithelium are very sensitive to roentgen radiation, much more so than the skin epithelium. The gill epithelium is one of the most sensitive types of epithelium in the adult axolotl. Even as little as 2,000 r, the smallest dose used, completely disorganized and destroyed the gill filaments and the gill epithelium, which were later replaced with skin epithelium containing many Leydig cells.

4. After irradiation with 8,000 r, giant cells developed in the skin epithelium that replaced the destroyed gill epithelium. Such giant cells were probably caused by moderate radiation damage to the peripheral skin epithelium.

5. Mitosis is extremely rare in the adult axolotl, but it was unusually frequent in close proximity to epithelial cells damaged by irradiation with 8,000 r. Evidently, this observation is an example of radiation stimulation.

6. In the lower vertebrates, and particularly the axolotl, radiation stimulation has previously been observed almost exclusively in young animals; mitosis has never before been observed as a result of radiation stimulation in adult axolotls. The stimulation mitotic activity following irradiation of the gills of adult axolotls in the present study is thus the first case of its kind.

7. A survey of the literature shows that sensitivity and response to radiation differ widely between different types of epithelium, especially skin epithelium and the epithelium of the internal organs, and may even differ widely for a single type of epithelium in young and adult animals.

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VOL. 99, NO. 2

SOME HISTORICAL NOTES ABOUT THE AMERICAN RADIUM SOCIETY*

By EDITH H. QUIMBY, Sc.D.
NEW YORK, NEW YORK

RADIUM was discovered by the Curies in 1896. In the next few years the physical properties of the radiations were studied, but it was not until the famous "Becquerel burn" in 1901 that the effects on living organisms were seriously considered. Becquerel had carried a glass tube of radium salt in his vest pocket, and was surprised to find a sore, like a burn, appear on his abdomen. Pierre Curie deliberately produced a similar reaction on his arm; this demonstration of the biological effects of the radiations led to animal experiments, and to the suggestion of the use of the rays in treatment of certain skin diseases. During the next 10 years the beginnings of radium therapy were made in a few institutions, and by a few private doctors.

Radium was extremely rare and expensive. The Austrian government had a monopoly on Bohemian pitchblende, which was the source of all the first available material. However, about 1910 a radium-bearing ore, carnotite, was found in the United States, not as rich as pitchblende, but much more abundant. In 1911 the Standard Chemical Company was formed in Pittsburgh to extract radium from this ore, and for 12 years they and two other American companies furnished a great part of the world's radium. Then extensive finds of pitchblende in the Belgian Congo put the American companies out of business, as far as production was concerned.

These companies, particularly the first one, were naturally interested in the development of radium therapy. The Radium Chemical Company, the distributors for the Standard Chemical Company, for a number of years published a monthly journal called Radium, edited by Dr. William H. Cameron, an internist, and Dr. Charles H. Viol, a chemist. Much of the early clinical work was published here, and both of the editors were among the founders of the American Radium Society.

On June 22, 1916, a group of doctors met in Detroit to consider organizing a society of those interested in radium therapy. A list of the members of this group has not been available, but they must all have come promptly to the new society, which was formally organized in Philadelphia on October 26, 1916. There were 20 charter members, 19 active and one (Dr. Viol) associate. A Constitution and Bylaws were adopted and officers elected, and the infant society was off to a good start. Its object was stated as "to promote the scientific and clinical application of radium and radioactive substances."

For the next 4 years the Society had 1 day meetings just preceding the American Medical Association meetings and in the same cities and by the end of this period the membership had grown to 71. In spite of the difficulties of war-time travel and the fact that several members were away on military duty in World War I, the meetings were well attended. Guests began to be attracted; many who came to visit stayed to apply for membership.

From the beginning, there were two classes of membership, active (M.D.s) and associate (workers in affiliated sciences). At first the only criterion for membership was interest in the clinical use of radium, but by 1919 professional qualifications were set for active members. These included reports of 25 cases treated with radium by the applicant. Associate members continued to be received on a basis of interest.

In 1921, a third category was established of honorary members. Much later, there

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.

was a revision of these classifications, so that nonmedical members could be made active, on recommendation of the Executive Committee. At that time also classes of inactive and senior members were established.

Dues started at $5.00 annually, and have increased over the years to meet increasing expenses, and also to pay for a subscription to the AMERICAN JOURNAL of ROENTGENOLOGY, RADIUM THERAPY & NUCLEAR MEDICINE, which in 1920 became the official organ of the Society.

By 1921, it was impossible to condense everything into 1 day, and a complete 2 day program was established. At that meeting there were 150 members and guests present, and there were 43 applications for membership, only 19 of which were accepted. In the ensuing years, there was some dissatisfaction with the Constitution and Bylaws, especially the one specifying the time and place of the meeting as the Monday and Tuesday preceding, and at the same place as, the annual meeting of the American Medical Association. From time to time minor changes were recommended but it was a good many years before a complete overhaul was accomplished.

In 1941, a committee was appointed to study a thorough revision of the Bylaws. At this time also it was mentioned that various members had suggested changing the name of the Society, since the activities were no longer those described in the preamble of the original Constitution or in more recent ones. Another important question which had arisen was the admission to membership of doctors not using radium. The committee polled the 187 active members of the society on these two matters; 143 replies were received. The majority vote was against change of name, and for admitting nonradium users.

There were no meetings in 1943, 1944, and 1945, because of the war. Thirty members were known to be in active service, and there were doubtless others. When meetings were resumed, the long-needed constitutional revision was submitted and voted upon. The Constitution adopted at that time does not differ greatly from the one in force today. One of the important Bylaw changes was to enable the Executive Committee to determine the time and place of the annual meeting, without reference to the American Medical Association or any other organization. The first independent meeting was held in 1953 in St. Louis, under the presidency of Dr. Howard Hunt. It was such a success that there has never again been a thought of hanging onto the coattails of another group. In fact, with a relatively small membership, the Society has been able to specialize in meeting in pleasant places.

Over the years, the membership increased steadily; in July, 1965 there were 483 active, inactive, and senior members. Of these, 273 indicated practice of some branch of radiology; 251 of these were diplomates of the American Board of Radiology. Seventy, 26, and 28 respectively reported surgery, oncology, and gynecology as their specialty; the remainder were scattered through half a dozen other specialties, or failed to report their fields. There were 21 honorary members, none of whom were residents of the United States. The total membership from the beginning was about 725; although efforts have been made to trace every member, they may not have been completely successful. There have been 46 honorary members elected; only 8 were citizens of the United States.

Scientific programs were of high caliber from the beginning. In the early years, a period was usually reserved for presentation of apparatus and new methods. It is of interest that in 1920, Dr. J. M. Martin presented a motion picture demonstration of cases of early and late carcinoma treated by means of radiotherapy.

The first stated objective of the Society was "to promote the scientific and clinical application of radium and radioactive substances." Over the years this was modified to bring in other sources of ionizing radiation; to limit treatment to "neoplastic and allied diseases," and finally to extend the

studies to physical and biological effects of the radiations, and to encourage liaison between the various specialties concerned with the treatment of cancer.

In the light of these objectives, it is interesting to look over the programs year by year. Although the interests of the founding and early members were mainly clinical, there has never been a meeting that did not have at least one nonclinical paper. These ranged through radiation physics, radiation biology, dosimetry, radiation hazards and protection, histology, various aspects of radioactive nuclides, and education and training. Of course, in the programs, certain clinical topics appear again and again; it is true that there is a limited number of anatomical sites or types of malignant disease to consider. However, through the years a review of abstracts for such papers shows that they were not reviews of old material, but were really reports of progress.

On the average, a program of 20 to 25 papers would consist of 15 to 20 which might be called "straight" clinical, and 2 to 4 each on topics such as clinical-biological, radio biological, radiophysical, and educational. As programs have become increasingly longer, about the same balance among classes of topics has been maintained. This year there are 54 papers—well assorted. New methods and new agents were regularly reported. Thus we find, in 1920 "intravenous injection of the active deposit of radium." (Many of the present members never even heard of this.) In 1929, there was a symposium on therapy with colloidal lead; in 1931, the first report on gold seeds; in 1937, induction of the artificial menopause and the use of estrogens in advanced cancer of the breast. In 1938, the brothers E. O. and John Lawrence brought the first information about production and use of radioactive phosphorus. Chemotherapy was first suggested in 1951, and after that there were few programs without some mention of it. The laser as a therapeutic instrument was introduced in 1965.

High energy x-rays, and other modalities for delivery of high energy radiations, such as neutrons, were discussed from 1933 on. Following the Lawrences' paper on radioactive phosphorus, some work with other radioactive nuclides was presented, but it was not until after World War II, with the development of the Atomic Energy Commission, that these substances began to play an important part in radiology. Beginning with 1951, papers on these substances formed part of every program.

Radiation hazards and radiation protection appeared intermittently from 1928 on. Dangers to both the patient and the doctor were considered.

Radiation biology was always of concern to the therapist. Action of radium rays on tissue, the effects of protraction and fractionation of the dose of radiation, and relative biological effectiveness of various radiations were considered at intervals from the beginning.

The determination of radiation dosage, first in terms of the energy emitted by the source, second in terms of the energy arriving at a particular organ or tissue, and, finally, in terms of that actually absorbed, has been a continuing topic of interest.

The Janeway Lecture as a very special part of the program merits particular mention. This honorary lectureship was established in 1933, in memory of a great pioneer in the field, Dr. Henry Harrington Janeway. Lecturers are selected because of their outstanding scientific contributions; their lectures have invariably been of the highest caliber, and directed to topics of special interest to the members of the Society.

Although the scientific programs presented at the meetings may be considered the most important part of the Society activity, some of the special committees have made outstanding contributions to the general field of radiotherapy. Early efforts at standardization of methods of radium treatments succeeded in bringing out the importance of primary and secondary filtration, and the need of listing all pertinent treatment factors for dosage specification.

A group was active for some time in developing protection standards, but when the American College of Radiology set up its Commission on Radiological Units, Standards, and Protection, it was realized that such a central group was better able to cover the field.

An Educational Committee (not always under that name) undertook various activities. One, in relation to the rental of radium to unqualified doctors, took on the nature of a crusade, but in the end its recommendations were published by practically all of the state medical journals and many others. It might be a bit hard to stop the rental of radium, but ethical groups could and did take a very strong stand against anyone giving directions for treatment of a patient whom the person giving the advice had not examined.

The matter of resident training in radium therapy was subject to a good deal of study over a period of years immediately after World War II. In 1949 a detailed program was put out, covering didactic lectures, physical laboratory exercises, and practical work in radiotherapeutic methods. Much of this is now regularly incorporated in resident training in recognized centers.

The American Board of Radiology has always been a special concern of the Society. In fact, it appears that the first suggestion of such a Board came from the Society in 1922, although nothing came of it at that time. The Board was actually organized in 1933, with the American Radium Society as one of the five sponsoring organizations, each of which had three members on the Board. Over the ensuing years, there was discussion between the Society and the Board as to the proper fields for examination and certification. Much of the time they were concerned with the inadequacy in radium training of many of the applicants for certification in radiation therapy. Specific ideas as to details of proper radium training were submitted to the Board. There had originally been a category for examination in radium therapy alone. Not more than a dozen doctors ever applied for it; it was early recognized that it represented an incomplete specialty, and it was dropped in 1955. The same thing happened to the category roentgenology; on the therapeutic side neither x-rays nor radium could be considered without relation to the other. Roentgen diagnosis was recognized as a category that could stand alone, but therapeutic radiology, or the whole field of radiology must perforce cover both x-ray and radium therapy. And in fact a few years later, as the radionuclides came into an important position, they also became an essential part of the therapy examination, with the strong support of the Radium Society.

Of course the Society, or its members, have taken part in many other activities, both immediately within the framework of the Society, and as inter-group procedures, with the American College of Radiology, the International and Inter-American Congresses of Radiology, the National Committee on Radiation Protection and others. Time does not permit any discussion of these. It would seem that enough has been said to make it evident that from a little acorn 50 years ago, quite a great oak has grown.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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Forty-ninth Annual Meeting: Royal York Hotel, Toronto, Ontario, Canada, May 29–31, 1967.

EDITORIALS

THE FORTY-NINTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Officers of the American Radium Society cordially invite you to attend the Forty-ninth Annual Meeting of the American Radium Society which will be held at the Royal York Hotel, Toronto, Canada, Monday, Tuesday and Wednesday, May 29, 30, and 31, 1967. The Scientific Program and Schedule of Events, which appear elsewhere in this issue of the JOURNAL, feature a number of new ideas and concepts relating to cancer. The Program has been enhanced by the gracious gesture of the Canadian Association of Radiologists which eliminated radiation therapy papers from its Spring Program in order to make them available to the American Radium Society. The membership of the Society should apply directly to the Royal York Hotel for reservations, specifying that they will be attending the Annual Meeting of the American Radium Society.

In addition to a number of distinguished foreign and American speakers, as well as five Symposia on interesting topics, there will be several unique features. Thus, two Panel Symposia will begin in the latter part of the morning session (one on Monday, May 29 and the other on Tuesday, May 30), during which period the panel members will present their respective expositions. Thereafter, luncheon for all members of the Society will be held in a designated room arranged with tables for ten members. At each table a host will guide the discussion of the morning's symposium toward the development of informed questions. The afternoon program will start with a discussion of the morning Panel Symposium based on the questions developed during the luncheon period.

Another feature will be audio-visual recording of the symposia and several other presentations. These recordings will subsequently become available for all educational purposes. Captain F. W. George, III, is Chairman of an *Ad Hoc* Committee which will prepare these films.

The Janeway Lecture will be delivered by Dr. R. Lee Clark, Jr. the Director and Surgeon-in-Chief of the M. D. Anderson Hospital, Houston, Texas.

The distinguished foreign guest speakers will be Dr. David Wallace of the Royal Marsden Hospital, London, England, who will discuss Cancer of the Bladder. Dr. Noel Wallace of the same institution will participate in the symposium on Testis Tumors. Dr. Julian Bloom, also of the same institution, will participate in the symposium on Brain Tumors in Children. Dr. J. C. Stewart of Christie Hospital and Holt Radium Institute will discuss The Place of Radiotherapy in the Management of Malignant Tumors of the Salivary Glands. Dr. Roger J. Berry of the United Churchill Hospital, Oxford, England, will present a paper on Some Observations on the Combined Effects of X-Rays and Methotrexate on the Reproductive Capacity of Tumor Cells *in Vitro* and *in Vivo*.

Dr. H. A. S. van den Brenk of Melbourne, will present the Dr. Gordon Richards Lecture, and the subject is Hyperbaric Oxygenation in Radiation Therapy. This lectureship has been awarded to this meeting of the American Radium Society by the Ontario Cancer Treatment and Research Foundation through the courtesy of Dr. W. G. Cosbie and his Canadian Colleagues.

The two Panel Symposia will be: Management of Stage I and II Carcinoma of the

Uterine Cervix; and Head and Neck Cancer. The five Symposia will include: Combination of X-Ray and Chemotherapy; Stem Cell Regeneration; Testis Tumors; Cancer of the Bladder; and Brain Tumors in Children.

The Scientific Program will be held daily from 9:00 A.M. to 5:00 P.M., as is the custom when meetings are held in a large city.

Dr. Clifford Ash and his Committee on Local Arrangements have arranged an outstanding Social Program. On Sunday evening, May 28, 1967, an informal welcoming reception will be held at the Royal York Hotel. If a play becomes available that Sunday evening, a theatre party may be organized. On Monday, May 29, 1967, there will be a luncheon and bridge party for the ladies and other guests at the Royal Canadian Yacht Club. On Tuesday, May 30, 1967, the ladies and other guests will be taken by special bus to Niagara Falls where a luncheon will be held in the Seagram Tower, a revolving dining hall which affords a magnificent panoramic view of the scenery. The Annual Banquet will be held Tuesday evening, May 30, 1967.

Registration will start at 12:00 NOON on Sunday, May 28, 1967, at the Royal York Hotel. Application forms for reservations will be mailed to all members of the Society and they should be returned promptly to the Royal York Hotel in order that the hotel and the Arrangements Committee may anticipate the number of registrants as far in advance of the meeting as possible. Registration will be automatic upon the receipt of your confirmed reservation inasmuch as the Arrangements Committee will receive a copy of each reservation from the hotel. Scientific Guests will be charged a nominal registration fee.

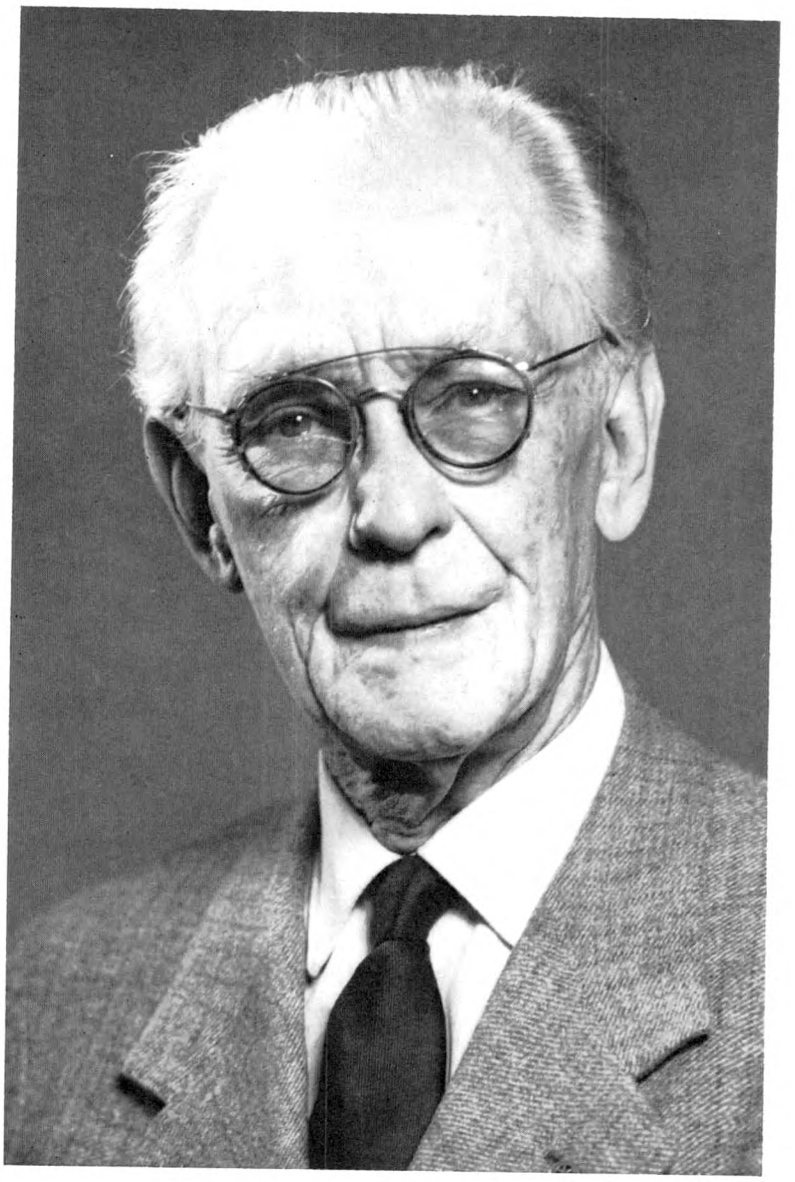
The Program booklet will be mailed to the members several weeks before the meeting in order that members may study the abstracts. Additional copies will be available at the Registration Desk at a slight cost.

Upon registering, each member will be assigned to the luncheon table where discussion of the Monday and Tuesday morning Panel Symposia will be held.

Tickets for the Annual Banquet will be sold at the Registration Desk. This Banquet, with its aura of good fellowship has always been a highlight of the meetings, and Dr. Ash's Committee has organized an entertaining evening.

Milton Friedman, M.D.
President, American Radium Society

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ELIS BERVEN
1885–1966

PROFESSOR ELIS BERVEN died on June 15, 1966 from a malignant tumor. He had been suffering from this disease for several years. It was, to some extent, a signal of overdosage of irradiation in the years when we had still limited knowledge of radiobiology.

Berven was a pioneer in radiotherapy and was for many years a leader of radiotherapy in the Scandinavian countries. He was born in Stockholm, Sweden, on March 4, 1885. After graduating from the Medical School of the Caroline Institute in 1913, he served as an assistant to the late Gösta Forssell at Radiumhemmet and devoted all his interest to this clinic. In the years 1923

to 1950, Berven was the Clinical Director of Radiumhemmet and of the Institute for Radiotherapy of the Caroline University, Stockholm. Several techniques for radiation treatment of malignant tumors were developed by Berven and his collaborators. His publications on carcinoma of the tonsils (1931), carcinoma of the head and neck (1929, 1936, 1950), carcinoma of the vulva (1949), carcinoma of the breast (1949) etc. are familiar to cancerologists all over the world. To a great extent the merit should be ascribed to Berven of having developed Radiumhemmet into one of the world's leading institutions for radiotherapy. Many colleagues have studied at his clinic and will with the greatest pleasure remember Berven as a great teacher, a fine doctor and a nice man. Personally, I worked with him since 1932 and it gave me great pleasure.

After retiring in 1950 from the Medical School, Berven devoted all his interest to the Swedish Cancer Society and served as a leader in clinical research until a week before he succumbed to the disease.

Professor Berven received many distinctions of honor. Thus, he became an Honorary Member of the American Roentgen Ray Society, the American Radium Society, the American College of Radiology, The Radiologic Society of North America, and of other organizations. In 1950 he received the degree of Honorary Doctor of Medicine at the University of Mainz.

The memory of Elis Berven will live for many years not only in Sweden but also in other countries.

H.-L. Kottmeier, M.D.

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THE AMERICAN RADIUM SOCIETY

PRELIMINARY PROGRAM

The following is the preliminary program arranged by the Scientific Program Committee for the Forty-ninth Annual Meeting of the American Radium Society to be held at the Royal York Hotel, Toronto, Ontario, Canada, May 29–31, 1967.

Sunday, May 28, 1967

9:00 A.M.–4:00 P.M.
Executive Committee Meeting.

12:00 NOON–6:00 P.M.
Registration.

Monday, May 29, 1967

8:00 A.M.–4:00 P.M.
Registration.

9:00 A.M.
Opening Ceremonies and Welcome Address, Forty-ninth Annual Meeting.
Claude T. Bissell, M.D., President, University of Toronto, Toronto, Ontario, Canada.

9:10 A.M.–9:25 A.M.
THE PRESIDENT'S ADDRESS—Milton Friedman, M.D. President, American Radium Society, New York University Schools of Medicine, New York, New York.

FIRST SCIENTIFIC SESSION
Charles G. Stetson, M.D., Chairman.
Mt. Sinai Hospital, New York, New York.

9:30 A.M.–9:45 A.M.
Immunotherapy for Trophoblastic Disease. W. D. Rider, M.D.,* B. Cinader, Ph.D.,* Ontario Cancer Institute, Toronto, Canada.

9:47 A.M.–10:02 A.M.
Laryngography in the Selection of Patients for Conservation Surgery in Supraglottic Cancer of Pharynx and Larynx. C. A. Perez, M.D.,* W. E. Powers, M.D., J. H. Ogura, M.D.,* S. Holtz, M.D., Washington University School of Medicine, St. Louis, Missouri.

10:04 A.M.–10:15 A.M.
Life Expectancy Reduction Factor as an Index for Reporting the End Results of Radiotherapy. K. C. Tsien, M.D., Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania.

10:17 A.M.–10:28 A.M.
Second Neoplasms in Children: Their Occurrence Following Therapy for an Unrelated Primary Tumor. M. Tefft, M.D.,* G. F. Vawter, M.D.,* The Children's Hospital Medical Center, Boston, Massachusetts.

10:30 A.M.
PANEL SYMPOSIUM: Management of Stage I and II Carcinoma of the Uterine Cervix.
Gilbert H. Fletcher, M.D., Chairman.
M. D. Anderson Hospital, Houston, Texas.
Participants:
S. B. Gusberg, M.D., Mount Sinai Hospital, New York, New York. The Management of Stage I and II Cancers of the Uterine Cervix.
Felix N. Rutledge, M.D., M. D. Anderson Hospital, Houston, Texas. Treatment of Stage I and II Adenocarcinomas of the Cervix.
David G. Decker, M.D., Mayo Clinic, Rochester, Minnesota. Sequential Radiation and Surgery in the Management of Stage I and II Carcinoma of the Cervix.
Fernando G. Bloedorn, M.D., University of Maryland Hospital, Baltimore, Maryland. The Treatment of Stage I and II Carcinoma of the Cervix.
Fred F. Durrance, M.D.,* M. D. Anderson Hospital, Houston, Texas. Radiotherapy Following Hysterectomy in Patients with Stage I and Stage II Cancer of the Cervix.
Alexander Brunschwig, M.D., Memorial Hospital, New York, New York. The Surgical Treatment of Cancer of the Cervix, Stages I and II.

12:00 NOON
Adjournment of First Scientific Session.

Luncheon Discussion.

SECOND SCIENTIFIC SESSION

1:30 P.M.–2:00 P.M.
Discussion of the Panel Symposium: Management of Stage I and II Carcinoma of the Uterine Cervix.

2:05 P.M.
Symposium: Combination of X-Ray and Chemotherapy. Roald N. Grant, M.D., Chairman.
American Cancer Society, New York, New York.

2:05 P.M.–2:18 P.M.
The Effect of Combined Chemotherapy and Irradiation on Bone Marrow Stem Cells. George G. Hibbs, M.D.,* Frank R. Hendrickson, M.D., Chicago, Illinois.

2:20 P.M.–2:40 P.M.
Some Observations on the Combined Effects of X-Ray and Methotrexate on the Reproductive Capacity of Tumor Cells *in Vitro* and *in Vivo;* A Radiobiologist's Schemes for Combining this Drug with Radiotherapy. Roger J. Berry,

* *By invitation.*

* *By invitation.*

M.D.,* United Churchill Hospital, Oxford, England.

2:42 P.M.–2:55 P.M.
Preoperative Irradiation Combined with 5-FU in the Treatment of Bladder Carcinoma. Justin J. Stein, M.D., Joseph J. Kaufman, M.D.,* University of California Center for the Health Sciences, Los Angeles, California.

2:57 P.M.–3:10 P.M.
Sequential Chemotherapy-Radiation Therapy of Buccal Mucosa Carcinoma. C. F. von Essen, M.D., L. B. M. Joseph, M.D.,* G. T. Simon, M.D.,* A. D. Singh, M.D.,* S. P. Singh, M.D.,* Christian Medical College and Hospital, Vellore, South India.

3:12 P.M.–3:25 P.M.
A Controlled Study of a Combination of 5-FU and Radiation in the Treatment of Malignant Neoplasm of the Gastrointestinal Tract. D. S. Childs, Jr., M.D., C. G. Moertel, M.D.,* M. A. Holbrook, M.D.,* R. J. Reitemeier, M.D.,* M. Y. Colby, Jr., M.D.,* Mayo Clinic, Rochester, Minnesota.

Joseph H. Farrow, M.D., Chairman.
Memorial Hospital, New York, New York.

3:30 P.M.–3:45 P.M.
Radiation Therapy Administered under Condition of Local Tissue Hypoxia for Bone and Soft Tissue Sarcomas of the Distal Extremities. Herman D. Suit, M.D., Robert D. Lindberg, M.D.,* M. D. Anderson Hospital, Houston, Texas.

3:50 P.M.–4:30 P.M.

The Annual Gordon Richards Lecture
Hyperbaric Oxygenation in Radiation Therapy. H. A. S. van den Brenk, M.D.,* Cancer Institute, Melbourne, Australia.

4:30 P.M.–4:40 P.M.
Discussion.
Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

5:00 P.M.
Adjournment of Second Scientific Session.

Tuesday, May 30, 1967

8:00 A.M.–4:00 P.M.
Registration.

8:15 A.M.
First Executive Session—for All Members.

Third Scientific Session

9:00 A.M.
Symposium: Stem Cell Regeneration.
Harold E. Johns, Ph.D., Chairman.
Ontario Cancer Institute, Toronto, Ontario, Canada.
Participants:

9:00 A.M.–9:13 A.M.
Normal Stem Cells. James E. Till, Ph.D.,* Princess Margaret Hospital, Toronto, Canada.

9:15 A.M.–9:28 A.M.
Leukemia Cells. Robert Bruce, M.D.,* Princess Margaret Hospital, Toronto, Canada.

9:30 A.M.–9:45 A.M.
Clinical Applications. Daniel Bergsagel, M.D.,* Princess Margaret Hospital, Toronto, Canada.

9:30 A.M.
Symposium: Testis Tumors.
Milton Friedman, M.D., Chairman.
New York University Schools of Medicine, New York, New York.
Participants:

9:30 A.M.–9:45 A.M.
Seminoma of the Testis. John G. Maier, M.D., Michael H. Sulak, M.D.,* Carl W. Boyer, M.D.,* Bernard T. Mittemeyer, M.D.,* Walter Reed General Hospital, Washington, D. C.

10:00 A.M.–10:13 A.M.
Tumors of the Testis. Noel Wallace, M.D.,* Royal Marsden Hospital, London, England.

10:15 A.M.–10:28 A.M.
Testicular Cancer: Management of Non-Seminomatous Germinal Tumors. Frederick W. George, III, M.D., S. S. Kurohara, M.D.,* R. F. Dykhuisen, M.D.,* N. L. Swensson, M.D.,* Allan F. Schroeder, M.D.,* Donald B. Vollman, M.D.,* U.S. Naval Hospital, San Diego, California.

10:30 A.M.–12:00 NOON
Panel Symposium: Head and Neck Cancer.
Richard H. Jesse, M.D., Moderator.
M. D. Anderson Hospital, Houston, Texas.
Participants:
Robert D. Lindberg, M.D.,* M. D. Anderson Hospital, Houston, Texas.
Frank R. Hendrickson, M.D., Presbyterian Hospital, Houston, Texas.
William E. Powers, M.D., Mallinckrodt Institute of Radiology, St. Louis, Missouri.
Benjamin F. Rush, Jr., M.D.,* University of Kentucky, Lexington, Kentucky.
Maurice Galante, M.D., University of California, San Francisco, California.

12:00 NOON
Adjournment of Third Scientific Session.

Luncheon Discussion.

Fourth Scientific Session

1:30 P.M.–2:00 P.M.
Discussion of the Panel Symposium: Head and Neck Cancer.
Marvin M. D. Williams, Ph.D.,* Chairman.
Mayo Clinic, Rochester, Minnesota.

2:00 P.M.–2:15 P.M.
Changes in Pulmonary Arterial Perfusion Following Therapeutic Radiation. Phillip M. Johnson, M.D.,* Robert H. Sagerman, M.D., Harold W.

* *By invitation.*

* *By invitation.*

Jacox, M.D., Columbia University, New York, New York.

2:17 P.M.–2:32 P.M.
Intraarterial Yttrium 90 Microspheres for Treatment of Carcinoid Tumors of the Liver. Norman Simon, M.D., Richard P. Warner, M.D.,* Murray G. Baron, M.D.,* Mt. Sinai Hospital, New York, New York.

2:34 P.M.–2:49 P.M.
An Evaluation of Radionuclides for Quantitative Bone Scanning. John S. Laughlin, Ph.D., Ernest J. Greenberg, M.D.,* David Weber, M.D.,* Peter Kenny, M.D.,* W. P. Laird Myers, M.D.,* Memorial Hospital, New York, New York.

2:50 P.M.–3:05 P.M.
A System of Dosimetry for Interstitial and Intracavitary Radiation Sources. Robert J. Shalek, Ph.D.,* George W. Batten, Ph.D.,* Marilyn Stovall, B.A.,* M. D. Anderson Hospital, Houston, Texas.

3:07 P.M.–3:17 P.M.
Preliminary Experience with Permanent Interstitial Implants Using Chromium 51 Sources. M. L. Griem, M.D., P. Lazarovits, M.D.,* P. Harper, M.D.,* The University of Chicago, Chicago, Illinois.

3:19 P.M.–3:29 P.M.
New Afterloading Technique for Interstitial Radiation Using Radioactive Microspheres. K. K. N. Chary, M.D.,* University of Minnesota Hospitals, Minneapolis, Minnesota.

3:30 P.M.–3:40 P.M.
Renal Protection in 2 Mv. Radiotherapy-A Technique Using Synchronously Rotating Absorbers. Ferdinand A. Salzman, M.D.,* Kenneth A. Wright, M.D.,* Magnus Smedal, M.D., John G. Trump, Sc.D., Lahey Clinic, High Voltage Research Laboratory, Boston, Massachusetts.

3:42 P.M.–3:52 P.M.
Irradiation of Multiple Giant Cell Tumors of Bone Superimposed on Paget's Disease. Alexander W. Pearlman, M.D.,* New York University Medical Schools, New York, New York.

4:00 P.M.–5:00 P.M.

THE JANEWAY LECTURE

R. Lee Clark, M.D.*
Director of M. D. Anderson Hospital, Houston, Texas.
Dr. Clark will be introduced by Dr. William S. MacComb.

5:00 P.M.
Adjournment of Fourth Scientific Session.

6:15 P.M.
Reception for all Members and Guests.
Host: Radium Chemical Company.

7:00 P.M.
Annual Banquet. Presentation of Janeway Medal. Entertainment.

Wednesday, May 31, 1967

8:15 A.M.
Second Executive Session—for All Members.
FIFTH SCIENTIFIC SESSION
John L. Pool, M.D., Chairman.
Memorial Hospital, New York, New York.

9:00 A.M.–9:13 A.M.
Radical Radiotherapeutic Management of Cervical Lymph Node Metastases from Cancers of the Head and Neck. Gerald E. Hanks, M.D.,* Malcolm A. Bagshaw, M.D., Henry S. Kaplan, M.D., Stanford University School of Medicine, Palo Alto, California.

9:15 A.M.–9:28 A.M.
The Influence of the Relationship "Local Tumor Extent-Time" Upon the Evolution of Tumors of the Nasopharynx. J. F. Bohorquez, M.D.,* St. John's General Hospital, St. John's, Newfoundland, Canada.

9:30 A.M.–9:43 A.M.
Paranasal Sinuses and Nasal Cavity Malignancies: Importance of Precise Localization of Extent of Disease. Max L. M. Boone, M.D.,* Thomas S. Harle, M.D.,* Howard W. Higholt, M.D.,* Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

9:45 A.M.–9:58 A.M.
Tonsillar and Peritonsillar Tumors: Their Treatment by Irradiation. Fernando G. Bloedorn, M.D., Morris J. Wizenberg, M.D.,* University of Maryland Hospital, Baltimore, Maryland.

10:00 A.M.–10:20 A.M.
The Place of Radiotherapy in the Management of Malignant Tumors of the Salivary Glands. J. C. Stewart, M.D.,* Christie Hospital and Holt Radium Institute, Manchester, England.

10:20 A.M.–10:28 A.M.
Discussion.

10:30 A.M.–10:40 A.M.
Persistent Tumor Cells in the Vaginal Smear after Radiation Therapy of Carcinoma of the Uterine Cervix: Prognostic Significance. Victor Marcial, M.D., Eduardo de Leon, M.D.,* Maria S. Blanco, M.D.,* Puerto Rico School of Medicine, San Juan, Puerto Rico.

10:42 A.M.
Symposium: Cancer of the Bladder.

10:42 A.M.–10:58 A.M.
Preoperative Irradiation with Cystectomy in the Treatment of Bladder Cancer. Ralph Phillips, M.D., Willet F. Whitmore, M.D., A. Ranald Mackenzie, M.D.,* John Iswariah, M.D.,* Harry Grabstald, M.D., Memorial Hospital, New York, New York.

* *By invitation.*

* *By invitation.*

11:00 A.M.–11:10 A.M.
Experience with Preoperative Irradiation for Bladder Cancer. Robert H. Sagerman, M.D., Presbyterian Hospital, New York, New York.

11:12 A.M.–11:52 A.M.
Cancer of the Bladder. David Wallace, M.D.,* Royal Marsden Hospital, London, England.

11:52 A.M.–12:00 NOON
Discussion.

12:00 NOON
Adjournment of Fifth Scientific Session.

SIXTH SCIENTIFIC SESSION

1:30 P.M.
Symposium: Brain Tumors in Children.
Arthur J. Holleb, M.D., Chairman.
Memorial Hospital, New York, New York.

1:30 P.M.–1:50 P.M.
The Prognosis and Treatment of Medulloblastoma in Childhood. Julian Bloom, M.D.,* N. K. Wallace, M.D.,* J. M. Henk, M.D.,* Royal Marsden Hospital, London, England.

1:52 P.M.–2:07 P.M.
Radiotherapy in the Management of Craniopharyngiomas. Further Experiences and Late Results. Simon Kramer, M.D., Carl Mansfield, M.D.,* Martha Southard, M.D.,* Jefferson Hospital Medical Center, Philadelphia, Pennsylvania.

2:10 P.M.–2:25 P.M.
Brain Tumors in Children.
Jean Bouchard, M.D., Royal Victoria Hospital, Montreal, Canada.

2:25 P.M.–2:35 P.M.
Discussion.

2:37 P.M.–2:47 P.M.
High Intensity Proximity Therapy of Intra-Oral Cancer. J. Ernest Breed, M.D., The Breed Radium Institute, Chicago, Illinois.

2:49 P.M.–3:02 P.M.
In Situ Lobular Breast Cancer: Clinical Consideration and Treatment. Joseph H. Farrow, M.D., Memorial Hospital, New York, New York.

3:04 P.M.–3:17 P.M.
Irradiation of Carcinoma of the Colon and Rectum. Robert J. Bloor, M.D., Carla A. Cook, M.D.,* Henry Ford Hospital, Detroit, Michigan.

3:19 P.M.–3:32 P.M.
Preoperative Irradiation in Rectal Cancer: Initial Comparison of Clinical Tolerance, Surgical and Pathologic Findings. Morton M. Kligerman, M.D., Marcos Tepper, M.D.,* Mark A. Hayes, M.D.,* Romeo A. Vidone, M.D.,* Yale University School of Medicine, New Haven, Connecticut.

3:35 P.M.–3:50 P.M.
Experience with Computerized Implant Dosimetry. J. G. Holt, M.D.,* G. Ragazzoni, M.D.,* S. Balter, M.D.,* Ulrich G. Henschke, M.D., B. Hilaris, M.D.,* Memorial Hospital, New York New York.

3:52 P.M.–4:02 P.M.
Contralateral Radiation Pneumonitis Following Ipsilateral Thoracic Irradiation. Colin Poulter, M.D.,* Philip Rubin, M.D., Division of Radiotherapy, University of Rochester, Rochester, New York.

4:04 P.M.–4:14 P.M.
Oxygen and L-Triiodothyronine in Radiotherapy of Mouse Tumors. Lucille A. duSault, A.B., Henry Ford Hospital, Detroit, Michigan.

4:16 P.M.–4:26 P.M.
Cancer of the Ovary—a 20 Year Study of 1,722 Patients Treated in the Ontario Cancer Clinics 1938–1958. John H. Maus, M.D., A. H. Sellers, M.D.,* E. N. Mac Kay, M.D.,* Medical Statistics Branch, Ontario Department of Health, Ontario Cancer Foundation, Windsor Clinic, Windsor, Canada.

4:28 P.M.–4:39 P.M.
The Microcirculation of the Lymph Node. Its Role in the Fourth Circulation. David L. Benninghoff, M.D., State University of New York, Brooklyn, New York.

4:40 P.M.–4:50 P.M.
Final Executive Session—for all Members and Installation of New Officers.
Adjournment of the Forty-ninth Annual Meeting of the American Radium Society.

* *By invitation.*

NEWS ITEMS

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Fifty-second Annual Meeting of the Radiological Society of North America held November 27–December 2, 1966 at the Palmer House in Chicago, Illinois, the following officers were elected: *President*—Harold G. Jacobson, M.D., New York, New York; *President-Elect*—Stanley M. Wyman, M.D., Belmont, Massachusetts; *First Vice-President*—John A. Campbell, M.D., Indianapolis, Indiana; *Second Vice-President*—Marvin M. D. Williams, Ph.D., Rochester, Minnesota; *Third Vice-President*—W. L. Sloan, M.D., Vancouver, British Columbia; *Secretary-Treasurer*—Maurice D. Frazer, M.D., Lincoln, Nebraska; and *Historian*—Howard P. Doub, M.D., Detroit, Michigan.

The *Chairman of the Board of Directors* is Herbert M. Stauffer, M.D., Philadelphia, Pennsylvania.

The Gold Medal of the Society was awarded to Juan A. Del Regato, M.D., Colorado Springs, Colorado.

The Fifty-third Annual Meeting of the Society will be held November 26–December 1, 1967 at the Palmer House in Chicago, Illinois.

SOUTHERN MEDICAL ASSOCIATION SECTION ON RADIOLOGY

The Section on Radiology of the Southern Medical Association announces the election of the following officers to serve for the year 1967: Raymond E. Parks, M.D., Miami, Florida, *Chairman;* W. H. Neil, M.D., Fort Worth, Texas, *Vice-Chairman;* and Andrew F. Giesen, Jr., M.D., Fort Walton Beach, Florida, *Secretary.*

These officers will be responsible for arranging the program for the Section on Radiology for the Sixty-first Annual Meeting of the Association, which will be held in Miami Beach, Florida, November 13–16, 1967. Anyone wishing to participate in the program should contact the Secretary of the Section, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Drawer M-M, Fort Walton Beach, Florida 32548.

Applications for scientific exhibit space can be obtained from Southern Medical Association, 2601 Highland Avenue, Birmingham, Alabama 35205.

THE AMERICAN SOCIETY OF RADIOLOGIC TECHNOLOGISTS

The Thirty-ninth Annual Convention of the American Society of Radiologic Technologists will be held June 10–15, 1967 at the Chase-Park Plaza Hotel, 212 N. Kingshighway, St. Louis, Missouri.

For further information please write to Sister Aloysius Marie, R.T., St. Mary's Infirmary, 1536 Papin Street, St. Louis, Missouri 63103.

NINETEENTH ANNUAL JOSEPH AND SAMUEL FREEDMAN LECTURE

On Saturday and Sunday, April 15 and 16, 1967, Dr. Richard H. Marshak, attending radiologist, Mt. Sinai Hospital, New York City, will deliver the Nineteenth Annual Joseph and Samuel Freedman Lecture in Diagnostic Radiology at the University of Cincinnati College of Medicine.

Radiologists desiring to attend are requested to write for further details to Dr. Benjamin Felson, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio, 45221.

POSTGRADUATE COURSE IN CHEST ROENTGENOLOGY

The 1967 postgraduate course, Chest Roentgenology, sponsored by the Department of Radiology, Medical College of Virginia will be held at the new Williamsburg Conference Center, a most modern, fully equipped meeting place set in the heart of one of America's great historic restorations, March 4–8, 1967.

This is a three-and-a-half day course

designed especially for the Clinical Radiologist and those physicians with a special interest in chest diseases. The course includes lectures, panel discussions and film interpretation conferences. With this arrangement, correlation of technical, physiologic, pathologic and clinical aspects of Chest Roentgenology can be encompassed. The course will be presented by members of the faculty of the Medical College of Virginia and by a group of distinguished guest faculty, well recognized for their contributions in these fields.

The Guest Faculty includes: Helen A. Dickie, M.D., Madison, Wisconsin; Theodore E. Keats, M.D., Charlottesville, Virginia; Ted F. Leigh, M.D., Atlanta, Georgia; Richard G. Lester, M.D., Durham, North Carolina; Averill A. Liebow, M.D., New Haven, Connecticut; Sidney W. Nelson, M.D., Columbus, Ohio; Laurence L. Robbins, M.D., Boston, Massachusetts; and E. G. Theros, LCDR, MC, USN, Washington, D. C.

For further information please write to Dr. M. Pinson Neal, Jr., Director, Postgraduate Course, Department of Radiology, Medical College of Virginia, 1200 East Broad Street, Richmond, Virginia 23219.

PEDIATRICS, PATHOLOGIC AND RADIOLOGIC SEMINAR

The Houston Society of Clinical Pathologists announces their Seventh Annual Seminar to be conducted by James B. Arey, M.D., Professor of Pathology, Temple University School of Medicine; Pathologist, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania; and John A. Kirkpatrick, Jr., M.D., Professor of Radiology, Temple University School of Medicine; Director of Radiology, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

The meeting will be on Saturday, April 22, 1967, 9:00 A.M.–4:00 P.M. at St. Luke's Episcopal-Texas Children's Hospital Auditorium, Houston, Texas.

For further details please contact Dr. John A. Webb, St. Luke's Episcopal Hospital, Texas Medical Center, Houston, Texas 77025.

SYMPOSIUM ON CURRENT CONCEPTS IN CHEST RADIOLOGY: PATHOPHYSIOLOGIC CORRELATIONS

The Department of Radiology of the University of Kentucky Medical Center is presenting a symposium on "Current Concepts in Chest Radiology: Pathophysiologic Correlations" from May 1 to May 5, 1967, just before the Kentucky Derby which is run on Saturday, May 6, 1967.

Roentgenologic findings will be discussed in terms of basic underlying pathologic mechanisms.

A distinguished Visiting Faculty and staff members of the College of Medicine of the University of Kentucky will participate in this symposium. A Film Seminar will be conducted at the end of each day.

The Visiting Faculty includes: Dr. William Anderson, University of Louisville School of Medicine; Dr. Mary Ellen Avery, Johns Hopkins Hospital, Baltimore, Maryland; Dr. Corning Benton, Cincinnati Children's Hospital, Cincinnati, Ohio; Dr. Robert G. Fraser, Royal Victoria Hospital, Montreal, Quebec, Canada; Dr F. H. Kemp, The Radcliffe Infirmary, Oxford, England; Dr. Sidney Nelson, Ohio State University College of Medicine, Columbus, Ohio; Dr. Eugene Robin, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Dr. F. W. Silverman, Cincinnati Children's Hospital, Cincinnati, Ohio; Dr. A. W. Templeton, University of Missouri Medical Center, Columbus, Missouri; and Dr. Jerry F. Wiot, Cincinnati General Hospital, Cincinnati, Ohio.

For further information please write to Dr. Harold D. Rosenbaum, Professor and Chairman, Department of Radiology, University of Kentucky Medical Center, Lexington, Kentucky 40506.

SYMPOSIUM ON DIAGNOSIS AND TREATMENT OF DEPOSITED RADIONUCLIDES

An International Symposium on the

"Diagnosis and Treatment of Deposited Radionuclides" will be held May 15–17, 1967, under the joint sponsorship of Battelle-Northwest, Hanford Occupational Health Foundation, Inc., and the U. S. Atomic Energy Commission.

The Symposium will consist of about 45 invited and submitted papers presenting information concerning the sources, incidence, diagnosis, treatment, and research related to accidental deposition of radionuclides in the body.

Dr. H. A. Kornberg, Manager, Biology, for Battelle-Northwest, and Dr. W. D. Norwood, President, Hanford Occupational Health Foundation, Inc., are Co-chairmen for the Symposium.

Topics to be covered include: Sources of Radioactive Materials that Can Enter the Body; Statistics on Human Cases; Magnitude of Deposited Radionuclide Problem Based on Future Usage; Properties of Radionuclides in Tissues; Basis of Diagnostic Procedures; Practices in Diagnostic Procedures; Fundamentals of Treatment for Deposited Radionuclides; Preferred Treatment Regimens for Various Contaminants and Modes of Exposures; and Legal Complication of Accidental Contamination and Treatment.

A series of informal "Workshop" discussions covering various aspects of the Symposium subject will be held Tuesday evening, May 16.

For further information please contact Dr. J. F. Park, P.O. Box 999, Richland, Washington 99352.

THE AMERICAN CANCER SOCIETY

The 1967 Scientific Session of the American Cancer Society will be held at the Sheraton-Dallas Hotel, Dallas, Texas on May 3, 1967.

The theme of the Session is: Current Concepts in Etiology and Diagnosis of Cancer.

The topics to be discussed include: Viruses and Vaccination in Cancer, James T. Grace, Jr., M.D., Buffalo, New York; Carcinogenic Effects of Tobacco Usage, Oscar Auerbach, M.D., East Orange, New Jersey; Carcinogenic Effects of Solar Radiation and Prevention Measures, Robert G. Freeman, M.D., Houston, Texas; The Carcinogenic Hazards of Diagnostic and Therapeutic Radiation, Justin J. Stein, M.D., Los Angeles, California; The Carcinogenic Hazards of Atomic Radiation, Elbert DeCoursey, M.D., San Antonio, Texas; Chemical Carcinogenesis, Paul Kotin, M.D., Bethesda, Maryland; What Constitutes an Adequate Periodic Health Examination? Emerson Day, M.D., New York, New York; The Case for Periodic Cancer Detection Examinations, Victor A. Gilbertsen, M.D., Minneapolis, Minnesota; An Evaluation of the Annual Checkup, Thomas W. Clark, M.D., Philadelphia, Pennsylvania; Proctoscopy for Cancer Detection in Asymptomatic Patients—What Age and How Often? Robert J. Rowe, M.D., Dallas, Texas; The Barium Enema in Cancer Checkups—Indications and How Often? Robert D. Moreton, M.D., Houston, Texas; The Pap Smear—What Technique and How Frequently? W. A. D. Anderson, M.D., Coral Gables, Florida; Present Role of Cytology in Cancer Detection (Exclusive of Uterine Cancer), William M. Christopherson, M.D., Louisville, Kentucky; Mammography for the Detection of Breast Lesions, Robert L. Egan, M.D., Atlanta, Georgia; Thermography and Zerography in Breast Diseases, Jacob Gershon-Cohen, M.D., Philadelphia, Pennsylvania: Lymphangiography in the Diagnosis of Cancer, Harry W. Fischer, M.D., Eloise, Michigan; and The Use of Radioisotopic Agents in the Diagnosis of Cancer, Norman B. Ackerman, M.D., Ph.D., Boston, Massachusetts.

For further information please write to Dr. Roald N. Grant, Director of Professional Education, American Cancer Society, Inc., 219 East 42nd Street, New York, New York 10017.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Textbook of Radiotherapy. By Gilbert H. Fletcher, M.D., Radiotherapist, Professor of Radiology, Head of Department of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Pp. 580, with 367 illustrations. Price, $20.00. Lea & Febiger, 600 S. Washington Square, Philadelphia, 1966.

There are many excellent textbooks presently available which discuss the various principles and practices of radiotherapy. Dr. Fletcher, however, has attempted to fill the need for a text which sets forth actual techniques of radiation treatment in such a way that they can be readily duplicated with ordinary facilities and technical assistance. He has succeeded admirably.

Most of the techniques described are currently in use at the M. D. Anderson Hospital and Tumor Institute. In addition, authors from other institutions throughout the world have contributed chapters dealing with their special areas of interest. The chapters are arranged by anatomic site and outline the contemporary application of radiation therapy to each of these regions.

Important general considerations and ancillary areas have not been ignored. Sections on dosimetry, radiation biology, treatment planning and special techniques are included, as well as such practical considerations as feeding and dental care in patients with head and neck cancer. The importance of combined surgical and radiation treatment is well documented by the contributions of several surgeons.

"The textbook has been written essentially for the trainees in radiotherapy," to quote the author, and it will prove invaluable to them; but general radiologists, radiotherapists and those surgeons interested in cancer will also find it to be of great interest.

Howard J. West, M.D.

BOOKS RECEIVED

Anatomy and Physiology for Radiographers. By C. K. Warrick, M.B., B.S.(Lond.), M.R.C.P., F.R.C.S.(E)., F.F.R., D.M.R., Radiologist-in Charge, Royal Victoria Infirmary, Newcastle upon Tyne; Lecturer in Radiology and Radiological Anatomy, University of Newcastle upon Tyne; Advisor in Radiology to No. 1 Regional Hospital Board and Honorary Advisor in Radiology to Sierra Leone. Second edition. Cloth. Pp. 280, with many illustrations. Price, 35/-net. Edward Arnold (Publishers) Ltd., 41 Maddox Street, London W.1, England, 1966.

Aortographie Abdominale (Tronc et Collatérales). By J. M. Cormier, Professeur agrégé à la Faculté de Médecine de Paris; C. Hernandez, Attaché de Radiologie des Hôpitaux de Paris; R. Kieny, Professeur agrégé à la Faculté de Médecine de Strasbourg, Chirurgien des Hôpitaux de Strasbourg; and J. Natali, Professeur agrégé à la Faculté de Médecine de Paris, Chirurgien des Hôpitaux de Paris. Paper. Pp. 120, with many illustrations. Price, 65 F. Masson & Cie, Éditeurs, 120, Boulevard Saint-Germain, Paris (VI), France, 1966.

Angiographie: Methoden, Indikation, Ergebnisse. Vorträge der Angiographietagung 18–20, November, 1965, in Baden-Baden. Herausgegeben by Prof. Dr. K. E. Loose, Chefarzt der Städt. Krankenanstalten Itzehoe/Holstein. Paper. Pp. 208, with 157 illustrations. Price, DM 56.-. Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1966.

Plattenepithelkarzinom der Mundhöhle: Grundlagen der Behandlung. By Prof. Dr. med. Dr. med. dent. B. Spiessl, Leiter der Kieferchirurgischen Abteilung des Bürgerspitals der Universität Basel. Paper. Pp. 200, with 112 figures. Price, DM 52.-. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1966.

Radiumbehandlung des Stimmband-Karzinoms. By Prof. Dr. Bernhard Minnigerode, Oberarzt der Universitätsklinik und -Poliklinik für HNO-Krankheiten, Göttingen. Cloth. Pp. 92, with 20 figures. Price, DM 30.-. Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1966.

Neuroradiologie. By Prof. MUDr. Dr. Sc. Jan Jirout, Röntgenabteilung der Neurologischen Klinik der Karls-Universität Prag. Cloth. Pp. 855, with 1069 illustrations. Veb Verlag Volk und Gesundheit, Berlin, 1966.

Annual Review of Nuclear Science. Emilio Segrè, Editor, University of California, Berkeley; Gerhart Friedlander, Associate Editor, Brookhaven National Laboratory; and H. Pierre Noyes, Associate Editor, Stanford University. Volume 16. Cloth. Pp. 671, with many illustrations and tables. Price, $8.50. Annual Reviews, Inc., 231 Grant Avenue, Palo Alto, Calif., 1966.

Biological and Biochemical Evaluation of Malignancy in Experimental Hepatomas. GANN Monograph 1, July, 1966. Proceedings of the U. S.-Japan Joint Conference, Kyoto, November 4–5, 1965. Cloth. Pp. 210, with some illustrations. Japanese Cancer Association, c/o Cancer Institute, Nishisugamo 2-chome, Toshima-ku, Tokyo, Japan, 1966.

Research Report on the Training of Radiological Physicists: A Study of British and Swedish Methods and their Relevance in the United States. Prepared by H. M. Parker of Pacific Northwest Laboratories, Division of Battelle Memorial Institute. Contract Number PH 86-66-8. Paper. Pp. 110. Division of Radiological Health, U. S. Department of Health, Education, and Welfare, Public Health Service, Bethesda, Md., 1966.

Alaryngeal Speech. By William M. Diedrich, Ph.D., Associate Professor in Speech Pathology, Hearing and Speech Department, School of Medicine, University of Kansas Medical Center, Kansas City, Kansas; and A. Youngstrom, Ph.D., M.D., Professor of Radiology, Radiology Department, School of Medicine, University of Kansas Medical Center, Kansas City, Kansas. Cloth. Pp. 220, with many illustrations. Price, $12.00. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1966.

Zonography: The Narrow-Angle Tomography. By D. Westra, Lecturer in Diagnostic Radiology, Radiological Institute of the University of Amsterdam. Translated by P. Westra and A. Smith Hardy. Paper. Pp. 82, with many illustrations. Price, $5.00. Excerpta Medica Foundation, Herengracht 119-123, Amsterdam, The Netherlands, 1966.

Conference on Murine Leukemia. National Cancer Institute Monograph 22, September, 1966. Sponsored by National Cancer Institute, National Institutes of Health, Bethesda, Md., and Albert Einstein Medical Center, Philadelphia, Pa. Edited by Marvin A. Rich and John B. Moloney. Cloth. Pp. 712, with some illustrations. Price, $6.25. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402, 1966.

Trends in Cancer Research. Paper. Pp. 84. World Health Organization, Geneva, 1966.

The Radiologic Clinics of North America. Symposium on The Biliary System. Guest Editor, Robert E. Wise, M.D. December, 1966, Volume IV, Number 3. Cloth. Pp. 203, with many illustrations. W. B. Saunders Company, West Washington Square, Philadelphia, Pa., 1966.

Nuklearmedizinische Laboratoriumsmethoden. Forward by Prof. Dr. med. Karl Oeff. Vorträge auf dem Kongress der International Association of Medical Laboratory Technologists, August 28–September 1, 1966, Berlin. Paper. Pp. 95, with some illustrations. Nuklearmedizinische Praxis und Forschung, Berlin, 1966.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual Meeting: Washington-Hilton Hotel, Washington, D. C., Sept 26–29, 1967.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Fernando G. Bloedorn, Division of Radiotherapy, University of Maryland Hosp., Baltimore, Md. 21201. Annual meeting: Royal York Hotel, Toronto, Ont., Canada, May 29–31, 1967.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Nov. 26–Dec. 1, 1967.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Century Plaza Hotel, Los Angeles, Calif., Jan. 31–Feb. 4, 1967.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit, Mich. 48201. Annual meeting: Atlantic City, June 18–22, 1967.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.
The Spring 1967 examination will be held at the Pittsburgh Hilton Hotel, Pittsburgh, Pennsylvania, June 5–9, inclusive. The deadline for filing applications for this examination was December 31, 1966.
The Fall 1967 examination will be held at the Statler Hilton Hotel, Dallas, Texas, December 4–8, inclusive. The deadline for filing applications is June 30, 1967.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo. 80907.

AMERICAN SOCIETY FOR DIAGNOSTIC ULTRASOUND
Secretary, Dr. Charles C. Grossman, 552 N. Neville St., Pittsburgh, Pa. 15213.

TWELFTH INTERNATIONAL CONGRESS OF RADIOLOGY
President, Dr. Kempo Tsukamoto, 9-1, 4-chome, Angewa, Chiba, Japan. Meeting: Hotel New Otane, Tokyo, Japan, Oct. 6–11, 1969.

NINTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907.
President, Dr. Leandro Zubiaurre, Montevideo, Uruguay. Meeting: Hotel San Rafael, Punta-del Este, Uruguay, Nov. 29–Dec. 5, 1967.

INTER-AMERICAN COLLEGE OF RADIOLOGY
President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.

AMERICAN SOCIETY FOR DIAGNOSTIC ULTRASOUND
Secretary, Dr. Charles C. Grossman, 552 N. Neville St., Pittsburgh, Pa. 15213.

ARIZONA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meetingsix months later.

ARKANSAS CHAPTER OF AMERICAN COLLEGE OF RADIOLOGY
Secretary-Treasurer, Dr. William J. Rhinehart, St. Vincent Infirmary, Little Rock, Ark. 72205.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary-Treasurer, Dr. Stanley Rogoff, Department of Radiology, University of Rochester Medical School, Rochester, New York 14620. Annual meeting: Temple University School of Medicine, Philadelphia, Pa., May 12–13, 1967.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Colonel Kurt Harrell, Landstuhl Army Medical Center, Landstuhl, Germany. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. R. John Gould, 441 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Arthur Lieber, University of Kentucky, University Hospital, Lexington, Kentucky. Meets quarterly.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Robert L. Pinck, Long Island College Hospital, 340 Henry St., Brooklyn, N. Y. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Victor A. Panaro, 42 Burroughs Drive, Buffalo, N.Y. 14226. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Friday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:00 NOON.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert A. Bornhurst, State Univ. Hospital, 750 E. Adams St., Syracuse, N. Y. 13210. Meets first Monday each month, October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Ollie E. Southard, 2787 Tudor Rd., Columbus, O. 43209. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Fredric D. Lake, 2548 N. Lakeview Ave., Chicago, Ill. 60614. Meets second Thursday of each month, October to April, except December, at the Pick-Congress Hotel at 8:00 P.M.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Cleveland Radiological Society
Secretary-Treasurer, Dr. Theodore J. Castele, 18869 Canyon Rd. Parkview Park, Ohio 44126. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

Colorado Radiological Society
Secretary, Dr. George F. Wertz, 1801 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, John S. Alexander, 1217 W. Cannon, Ft. Worth, Tex. Meets monthly, third Monday, at Southwest International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Radiological Society
Secretary, Dr. Tom H. Piatt, 12 Camino Encinas, Orinda, Calif. 94563. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. T. F. Haase, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

Eastern Radiological Society
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

Florida Radiological Society
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

Georgia Radiological Society
Secretary, Dr. Al Rayle, Jr., 938 Peachtree St., N. E., Atlanta, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Miami Radiological Society
Secretary-Treasurer, Dr. Arthur R. Miller, North Miami General Hospital, 1701 N.E. 127th St., North Miami, Fla. Meets monthly, third Wednesday at 8:00 P.M., at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, John W. Fries, 3520 Chippewa St., St. Louis, Mo. 63118.

Hawaii Radiological Society
Secretary-Treasurer, Dr. Donald Ikeda, Kuakini Hospital, 347 N. Kuakini St., Honolulu, Hawaii 96817. Meets third Monday of each month at 7:30 P.M.

Houston Radiological Society
Secretary, Dr. William A. Vint, 1004 Seymour, Pasadena, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Horne, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter, American College of Radiology
Secretary-Treasurer, Dr. Robert H. Greenlaw, Dept. of Radiology, Univ. of Kentucky Med. Ctr., Lexington, Ky. Meets semiannually.

Kentucky Radiological Society
Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Samuel Gelband. Meets second Tuesday of the month in February, April, June, October and December.

Los Angeles Radiological Society
Secretary, Dr. Norman Zheutlin, 8720 Beverly Blvd., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society
Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Waterville, Me. Meets in June, September, December and April

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building. Baltimore, Md.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Indiana. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Donald P. Babbitt, 1700 W. Wisconsin Ave., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Edward A. Peterson, 572 Lowry Medical Arts Bldg., St. Paul, Minn. Meets twice annually, fall and winter.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

Missouri Radiological Society
Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nebraska State Radiological Society
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month, October through May, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. William G. McPheron, Hobbs, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society
Secretary, Dr. Arnold L. Bachman, Francis Delafield Hosp., 99 Fort Washington Ave., New York, N. Y. 10032. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Meeting: Waldorf Astoria Hotel, N. Y., April 27–29, 1967.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. Robert J. Olson, 1240 8th Ave., Williston, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary-Treasurer, Dr. John Turner, 1215-28th St., Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Mortimer Lubert, Mt. Sinai Hospital, Cleveland, Ohio. Annual meeting to be announced.

Oklahoma State Radiological Society
Secretary, Dr. Robert Sukman, 1200 N. Walker, Oklahoma City, Okla. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. George W. Logan, 301 Newport Blvd., Newport Beach, Calif. Meets fourth Tuesday of every month at Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. Irving J. Horowitz, 2311 N.W. Northrup Str., Portland, Ore. 97210. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Willis Taylor, 1118 9th Ave., Seattle, Washington. Annual meeting to be announced.

Pennsylvania Radiological Society
Secretary, Dr. T. Frederick Weiland, 619 Ridgeway Ave., Grove City, Pa. Annual meeting to be announced.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Robert N. Berk, 9100 Babcock Blvd., Pittsburgh, Pa. 15237. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

Radiological Society of Connecticut, Inc.
Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450 Chapel St., New Haven 11, Conn. Meetings are held quarterly.

Radiological Society of Greater Cincinnati
Secretary, Dr. Harold N. Margolin, 6159 Tulane Road, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Lester W. Eavenson, 2700 Napoleon Ave., New Orleans 15, La. Meets semiannually, during Louisiana State Medical Society meeting and 6 months later.

Radiological Society of New Jersey
Secretary, Dr. John W. Marquis, 12 Hawthorne Ave., East Orange, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island
Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Gerald M. McDonnel, U.C.L.A. Medical Center for Health Sciences, Los Angeles, Calif. 90024. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Irving B. Joffe, Rochester General Hospital, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting: Brown Palace, Denver, Colo., Aug. 17–19, 1967.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles P. Hyslop, 7901 Frost St., San Diego 22, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. H. Joachim Burhenne, Children's Hospital and Adult Medical Center, 3700 California St., San Francisco, Calif. 94119. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco, Calif. 94118.

Santa Clara County Radiological Society
Secretary, Dr. Bill G. Karras. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Gregory T. Henesy, 915 19th St., N. W., Washington, D. C. 20006. Meets at Medical Soci-

ety Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. 32548. Annual meeting: Miami Beach, Fla., Nov. 13–16, 1967.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY
Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Washington Hilton Hotel, Washington, D. C., Sept. 25, 1967.

SOCIETY OF NUCLEAR MEDICINE
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Seattle, Wash., June 20–23, 1967.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Carleton J. Wright, 2015 Clarman Way, San Jose, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

SOUTHERN RADIOLOGICAL CONFERENCE
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting to be announced.

SOUTHWESTERN RADIOLOGICAL SOCIETY
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. E. K. Carter, Holston Valley Community Hosp., Kingsport, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting to be announced.

TRI-STATE RADIOLOGICAL SOCIETY
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Carlisle C. Smith, Salt Lake General Hospital, 2033 S. State St., Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. George G. Green, Morgantown, W. V. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Arnold Gerson, Medical Arts Bldg., Mt. Vernon, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. 53209. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY
Secretary, Dr. Ronald R. Lund, 240 W. 9th St., Casper, Wyo. Meets in fall with State Medical Society and in spring on call of President.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador.

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPÍA CUBANA
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A.C.
Coahuila No. 35, México 7, D. F.
Secretary-General, Dr. Armando L. Rodríguez
Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLÓGICA PANAMEÑA
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

SOCIEDAD RADIOLÓGICA DE PUERTO RICO
Secretary, Dr. José T. Medina, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY
Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May. Annual meeting: Central Hall and Caxton Hall, Westminster, London, S. W. 1., England, April 26–28, 1967.

CANADIAN ASSOCIATION OF PHYSICISTS, DIVISION OF MEDICAL AND BIOLOGICAL PHYSICS.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY
Secretary, Dr. B. V. Evans, 105 Northgate Bldg., Alberta, Canada. Meets second Tuesday of each month in various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting Guy's Hospital, London, June 23–24, 1967.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS IN IRELAND
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 p.m. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Maurice Dufresne, *Associate Honorary Secretary-Treasurer*, Dr. F. Robert MacDonald, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Skyline Hotel, Toronto, Canada, Feb. 28–March 5, 1967.

Montreal Radiological Study Club
Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie
Secretary General, Dr. Jacques Lespérance, 5415 Boul. L'Assomption, Montreal 26, P. Q., Canada. Meets every third Tuesday from October to April. Annual meeting: Oct. 12–14, 1967.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. T. P. Loneragan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 p.m. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Miguel Mario Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia
Secretary-General, Dr. Eduardo E. Navarrine, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Boliviana de Radiología
Secretary, Dr. Héctor Fernández Ferrufino, Casilla 1192, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Patricio Barriga, Casilla 13426, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary-General, Dr. Armando Uribe, Hospital Militar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary-General, Dr. Augusto Cáceres G. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologica del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedad de Radiología de El Salvador
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Luis F. Muro, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie
General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France.
General Secretary, Dr. H. Ludin, Department of Roentgenology, Basler Kinderspital, Basel, Switzerland. Annual Meeting: Basel, Switzerland, April 13–17, 1967.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

Scandinavian Association for Medical Radiology
Secretary-General, Dr. C-E. Unnérus, Hagalund-Tapiola, Havsvindsvägen 5 C., Finland. Annual meeting: Umeå, Sweden, 1967; Copenhagen, Denmark, 1968.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Juan Gomez Lopez, Villanueva, 11, Madrid 1. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid. Annual general meeting to be announced.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah I Diakarta, Indonesia

Iranian Radiological Society
Secretary, Dr. Issa Yaghmai, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

King, E. G., Wood, D. E., and Morley, T. P. The use of macroaggregates of radioiodinated human serum albumin in brain scanning. *Canad. M. A. J.*, Aug. 27, 1966, *95*, 381–389. (From: Division of Neurosurgery, and the Division of Nuclear Medicine, Toronto General Hospital, Toronto, Ontario, Canada.)

Intra-arterially injected macroaggregates of radioiodinated human serum albumin were used in the experimental detection of brain tumors in mice, and in a small group of human subjects.

Mice bearing transplants of ependymoblastoma were given tracer doses of MAA of average particle size 29 μ. Tissue distribution studies showed brain/tumor ratios ranging from 43.5 to 1 immediately, to 2.1 at two hours. The authors felt that particles trapped in tumor circulation tended to remain in place longer than those within normal vessels.

In a second group of mice the arterial circulation of the ear was studied microscopically *in vivo*, and decay of the entrapped particles was followed. Blockade of arterioles and reversal of flow were observed. Capillary beds were seen to shut down for short periods—a phenomenon which may occur in the mouse ear under normal circumstances.

The authors then turned their attention to a group of 12 patients with known or presumed brain tumors. A scanning was done on each of them employing doses of I^{131}MAA of the order of 20–30 μc. Total quantity of particulate matter was estimated to be from 0.25 to 1.0 mg. Four of the 12 patients had complications ranging from focal seizure to increasing neurologic deficit, and at least 3 of these could be attributed directly to the injection of MAA. The clinical trial was then terminated.

Scans were of modest quality and only 6 of the tumors were demonstrated objectively.—*Frederick J. Bonte, M.D.*

Roig, Juan, Moss, William T., and Quinn, James L., III. Usefulness of the brain scan in therapeutic radiology. *Radiology*, June, 1966, *86*, 1082–1084. (From: Departments of Radiology, Northwestern University Medical School, and Therapeutic Radiology, Chicago Wesley Memorial Hospital, Chicago, Ill.)

The accurate localization of intracranial neoplasms as well as a simple assessment of tumor response are essential to modern therapeutic radiology. Until recently the radiotherapist had no satisfactory diagnostic aid for exact portal placement in the treatment of single or multiple intracranial neoplasms, or for the re-treatment of recurrent or persistent brain tumors. Since conventional and special roentgenographic studies and even craniotomy are often inconclusive as to tumor location, the advent of the brain scan has aided greatly in the evaluation of intracranial neoplasms as to their location as well as diagnosis, making exacting localization possible. The purpose of the authors is to report their experience with the brain scan in planning and follow-up of cranial radiotherapy.

Of 70 patients given radiotherapy for intracranial neoplasms, brain scan localization of these tumors was judged good in 48, fair in 9 and noninformative in 13 cases. The radiopharmaceuticals used in this series included chlormerodrin Hg^{203}, chlormerodrin Hg^{197} and Tc^{99m} in the chemical form pertechnetate.

Three exemplifying cases are presented which illustrate the value of brain scans in the conduct and evaluation of radiation therapy. Since good or fair localization was obtained in 80 per cent of the cases, exact portal placement was made possible. In some cases, *e.g.*, frontal lobe tumors, the knowledge of the localization is important because higher doses can be delivered without compromising essential cerebral function. The determination of whether a lesion is single or multiple is important in planning therapy in patients with intracranial metastases. The brain scan also allows the radiotherapist to evaluate the responsiveness of the treated tumors.

The brain scan is most effective in the localization and the follow-up of glioblastomas and cerebral astrocytomas which accounted for 75 per cent of the tumors in this series. Certain types of neoplasms, such as posterior fossa, brain stem, pituitary and base of brain neoplasms showed poor localization. These accounted for the majority of the nonlocalizing tumors in this series.—*Paul M. Kroening, M.D.*

Gyepes, M. T., and D'Angio, G. J. Extracranial metastases from central nervous system tumors in children and adolescents. *Radiology*, July, 1966, *87*, 55–63. (From: Department of Radiology and the Children's Cancer Research Foundation, The Children's Hospital Medical Center; and the Department of Radiology, Harvard Medical School, Boston, Mass.)

Remote metastases from tumors of the brain and spinal cord and their coverings are rare but do occur. The authors report 8 cases, 7 in children and 1 in an adolescent exhibiting this complication. These cases are described in detail. Five of the tumors were primary in the posterior fossa (3 medulloblastomas and 2 neuroblastomas); 2 were meningeal sarcomas; and 1 was considered to be a glioblastoma multiforme.

There has been considerable speculation and discussion about the reason for the rarity of remote metastases. Since there are no lymphatics in the brain or spinal cord, central nerve system tumors cannot spread via lymphatic pathways while confined within the brain or spinal cord. Lymphatic

permeation becomes possible only when there is extension of tumor to the covering membranes. Blood vessels are rarely invaded by tumors primary in the brain and spinal cord. This has been attributed to compression of thin-walled vessels by growing tumor.

Surgical procedures antedated the identification of metastases in all but a few of the recorded cases. It seems that surgery breaks down the "barrier" to metastases. This could be due to: (1) opening of vascular channels so they become accessible to tumor cells; (2) capillary proliferation as part of the reparative process providing access for metastatic cells; and (3) decreased compressibility of vessels in the glial scar making them more susceptible to invasion.

In most instances metastases appeared within 1–2 years after primary diagnosis at surgery. The radiographic appearance of bone metastases is usually nonspecific. Osteolytic, osteoblastic, and mixed metastases have all been reported.—*A. W. Sommer, M.D.*

Glasgow, Joseph L., Currier, Robert D., Goodrich, Jack K., and Tutor, Forrest T. Brain scans at varied intervals following C.V.A. *J. Nuclear Med.*, Dec., 1965, *6*, 902–916. (From: Veterans Administration Center, and University Medical Center, Jackson, Miss.)

Experience with Hg^{203} brain scans following cerebrovascular accidents (C.V.A.) is reported. The series is small: 71 patients, and only 88 scans were obtained.

Serial scannings were not advisable because of the relatively high radiation dose to the kidneys. Varying the intervals at which scannings were performed was deliberate and repeat scans were obtained in 17 cases. Another 58 cases, with scannings made prior to the initiation of this study, and in which a final diagnosis of cerebrovascular accident was made, were added.

The results show positive scans in 41 per cent of cases and no positive scan was obtained 6 months post-ictus. Scans done within the first 28 days were positive in 50 per cent of cases, and in scans done between 15–28 days post-ictus the peak of 72 per cent of positive scans was reached when done during the third week. Considering middle cerebral artery territorial infarcts only 2 of 5 were positive when done during the first week. When scanned between 8 and 28 days, 19 of 22 or 86 per cent were positive, thus indicating that a time lag is important in demonstrating infarcts on brain scan.

The localization of an infarct tended to be more irregular, than that of a tumor, when scanned early, with diffuse ill-defined borders. The concentration in the infarcted area was no more than that of the scalp or muscles. With passage of time the area of localization became smaller and sharper and at times resembled a tumor. The evolutionary changes ranged from 2 to 3 weeks or as long as 3 to 4 months. Too few serial studies have been done but the limited data indicate that evolutionary changes may have diagnostic value.

The mechanism of the uptake has been explained by several theories, as for instance: breakdown of the blood brain barrier, with increased capillary permeability; cerebral edema of surrounding tissue with accumulation of the radioactivity in the interstitial fluid; and increased vascularity. The latter theory, increased vascularity, could account for the time lag to develop positive scans and also could give an indication why the concentration in the scans is usually no greater than that of normal vascular structures, *i.e.*, the scalp and muscles.—*Richard T. Browne, M.D.*

Pribram, H. F. W. Selective catheterization of the external carotid artery. *Radiology*, Aug., 1966, *87*, 315–320. (From: Department of Radiology, University Hospitals, Iowa City, Iowa.)

The author presents an interesting ancillary approach to cerebral angiography consisting of the capability of selective catheterization of the external carotid artery, following routine carotid angiography.

The advantage of this angiographic capability is that it avoids the sometimes confusing superimposition of simultaneous internal and external carotid artery opacification. The technique permits the differentiation of extrinsic from intrinsic cerebral tumors (both supra- and infratentorial) and is particularly useful in clarifying those deceptive meningiomas which depart from their usual dual blood supply. The method also aids in the diagnosis of nasopharyngeal angiofibromas and glomus jugulare tumors and in demonstrating the external carotid blood supply of intracranial angiomas. Also, metastases can be identified as to an extracerebral location and extradural and subdural hematomas may be differentiated.

The author's technique of selective transcarotid catheterization of the external carotid artery is accomplished by the initial introduction of a 19 gauge teflon catheter needle into the common carotid artery for routine cerebral angiography from either the common or internal carotid arteries. Should this study indicate a need for selective catheterization of the external carotid artery, the tip of the teflon catheter is withdrawn to below the carotid bifurcation and a short guide wire with a gentle curve at the tip is introduced through the catheter. Usually, this gentle curve of the guide wire allows it to pass into the external carotid artery without difficulty, whereas an excessive curve facilitates passage into the superior thyroid artery. The proper placement of the wire is confirmed by image intensification and the catheter is introduced into the artery over the wire, which is then withdrawn. If the carotid bi-

furcation is high in the neck and the original teflon catheter is not long enough, it is replaced with a 30 cm. long polyethylene catheter which is subsequently introduced into the external carotid artery. —*Edward B. Best, M.D.*

Neck and Chest

Elston, C. W. Pneumonia due to liquid paraffin: with chemical analysis. *Arch. Dis. Childhood*, Aug., 1966, *41*, 428–434. (From: Department of Morbid Anatomy and Histopathology, Charing Cross Hospital Medical School, London W.C.2, England.)

Following a brief review of the literature of oil aspiration pneumonia the author presents a case report of fatal pneumonia due to oral administration of liquid paraffin (mineral oil).

The patient was a newborn with multiple congenital anomalies, including esophageal atresia and tracheo-esophageal fistula (which were surgically corrected), bladder neck atresia and hydronephrosis. Death occurred at the age of 9 months, the last 6 months of which mineral oil was administered almost continuously on a daily basis in doses of 8 to 45 ml.

Since mineral oil is not identifiable by histologic or histochemical technique, a method is given for extraction and purification with subsequent analysis of refractive index and infrared spectrum as a means of accurate identification.—*Donald S. Linton, Jr., M.D.*

Davis, Constance M. Inhaled foreign bodies in children: an analysis of 40 cases. *Arch. Dis. Childhood*, Aug., 1966, *41*, 402–406. (From: Royal Liverpool Children's Hospital and Alder Hey Children's Hospital, Liverpool, England.)

A complete analysis of pertinent clinical and roentgenographic findings is given in a series of 40 children who presented with acute foreign body inhalation.

Approximately one-half of the children were under 3 years of age and one-quarter were under 2 years of age.

The distribution of the foreign bodies in the tracheobronchial tree showed only 2 of the 40 in the trachea itself, whereas 15 were in the right main-stem bronchus, 13 in the bronchus intermedius or right lower lobe bronchus, 7 in the left main-stem bronchus and 2 in the left lower bronchus.

A relevant history of the inhalation was present in 26 of the 40. The foreign body was densely opaque in 7 cases, and faintly opaque in 4.

The commonest roentgenologic finding was unilateral basal collapse or consolidation. This was not found to be specific however, as the foreign body was present in a location other than the lower lobe bronchus.

Obstructive emphysema was present in 5 patients, including 1 case in which the foreign body was in the trachea and both lungs were emphysematous.

The author feels that if the radiologist is aware of the possibility, he should find confirmatory evidence on the chest roentgenogram in nearly every case where foreign body is present.—*Donald S. Linton, Jr., M.D.*

Wenz, W., Wolter, H. H., and Trede, M. Das "Scimitar-Syndrom": Fehleinmündende rechte Lungenvene, Dextroversion des Herzens und Hypoplasie der Lunge. (The scimitar syndrome: abnormal course of right pulmonary vein, dextroversion of the heart and hypoplasia of the lung.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1966, *105*, 177–184. (Address: Priv.-Doz. Dr. W. Wenz, Chirurgische Univ.-Klinik, 69 Heidelberg, Germany.)

The scimitar sign may be easily visible on a routine roentgenogram of the chest as a broad band of increased density parallel to the curvature of the right cardiac border increasing in width in its course downwards towards the inferior vena cava. The scimitar syndrome consists of anomalous insertion of the pulmonary veins, hypoplasia of the right lung and dextroversion of the heart. Partial anomalous flow is more common than total anomalous insertion, most frequently into the inferior vena cava. The dextroversion of the heart may be secondary to the pulmonary hypoplasia or it may be a congenital anomaly. Right-sided involvement occurs twice as often as left-sided anomalies. Due to the abnormal hemodynamics, hypertrophy and dilatation of the right ventricle and right auricle occur and there is an atrial septal defect with a left-to-right shunt. The condition may be better demonstrated in tomographic sections but should be confirmed by cardiac catheterization and angiocardiography.

Surgery is indicated in the presence of right-sided cardiac failure or to prevent serious infections in a lung subject to degenerative changes and progressive bronchiectasis. Three methods of surgery are possible: (1) If the venous stem adjacent to the anomalous insertion has a branch communicating with the left atrium, simple ligation of the former suffices; (2) if the anomalous insertion is close to a low-lying atrial septal defect, both openings can be closed by suture or plastic material and a transplant is constructed so that the venous blood flows into the left auricle; and (3) in the remaining cases, the anomalous insertion into the inferior vena cava is tied off and transplanted by an end-to-side anastomosis into the left atrium.—*J. Zausner, M.D.*

Lopez-Majano, Vincent, Tow, Donald E., and Wagner, Henry N., Jr. Regional distribution of pulmonary arterial blood flow in

emphysema. *J.A.M.A.*, July 11, 1966, *197*, 81–84. (From: Department of Radiological Science, Johns Hopkins Medical Institutions, and Veterans Administration Hospital, Baltimore, Md.)

This article deals with the use of macroaggregated iodinated I^{131} serum albumin and scanning as a safe, simple, and useful method to demonstrate decreased pulmonary arterial blood flow in patients with emphysema. It may also offer a means of differentiating emphysema from chronic bronchitis and asthma, as in these latter two the scans are normal. The method is furthermore helpful in evaluating patients for surgery and to follow-up the results of surgery.

The problems related to the diagnosis of emphysema both clinically and by the various laboratory tests are reviewed. The need to resort to tomography and angiocardiography to show the vascular changes not demonstrated on chest roentgenograms is mentioned. Since the smaller vessels can not be seen on tomography and the vascular changes are usually at the capillary level this method is of limited value.

Radioactive gases have been used with some success to show focal abnormalities of both ventilation and perfusion in patients with emphysema. This work has suggested that demonstration of these areas would be of value in selecting patients in whom lung function might be improved by surgery. Lung scanning is safe and easy and permits evaluation of blood flow up to and including the capillaries.

Sixty-two patients were scanned after careful clinical history and pulmonary function studies. Three hundred μc I^{131} serum albumin was given intravenously and quantitative regional pulmonary blood flow was determined.

The results showed that there was uneven distribution of pulmonary blood flow in most patients.

The findings could be divided into four groups: (1) patchy, 71 per cent; (2) unilateral, 11 per cent; (3) unilateral patchy, 13 per cent; and (4) normal, 5 per cent.

No correlation between regional distribution of involvement on scans and various clinical and functional manifestations could be made.

The possible mechanisms of well localized involvement in patients with generalized emphysema as demonstrated by others with tomography and Xe^{133} and confirmed by this study are reviewed.—*Richard T. Browne, M.D.*

Kavanagh-Gray, Doris. Factitious aortic valve insufficiency. *Canad. M. A. J.*, Aug. 20, 1966, *95*, 354–356. (From: Clinical Investigation Unit, St. Paul's Hospital, Vancouver, British Columbia, Canada.)

Conflicting statements appear in the medical literature concerning the frequency of "factitious" aortic insufficiency, a condition in which there is angiographic, but no clinical, evidence of aortic regurgitation. Some regard this entity as an artefact and conclude that if the examination is conducted with proper attention to technique factitious aortic insufficiency should not be encountered. Two factors appear important in this respect: (1) the catheter should not impinge forcibly on the valve leaflets disturbing their natural function; (2) a closed-end, multiple side-holed, relatively straight catheter should be used to prevent the "jet" effect from the tip or from the side holes during recoil. However, even when strict attention has been paid to details of angiographic technique, factitious aortic insufficiency still has been noted.

Two patients are reported who had angiographic evidence of aortic insufficiency but no clinical evidence of aortic regurgitation. At operation for mitral valve replacement and at autopsy, the aortic valves appeared normal in both of these patients. These observations support the contention that factitious aortic insufficiency may be encountered despite careful attention to the technical details of aortography.—*Douglas S. Kellogg, M.D.*

Soulen, Renate L., Lapayowker, Marc S., and Gimenez, Jose L. Echocardiography in the diagnosis of pericardial effusion. *Radiology*, June, 1966, *86*, 1047–1051. (From: Department of Radiology, Temple University Medical Center, Philadelphia, Pa.)

The authors describe their technique, possible sources of error, and their results in utilizing reflected ultrasound for detection of pericardial effusions. The basic method is the production of high frequency wave impulses from a 2.5 megacycle transducer applied to the anterior chest wall over the left ventricle at such a position and angle that the wave impulses strike the posterior wall of the left ventricle at or close to the perpendicular. Thus the higher amplitude reflected wave impulses ("echoes") return to the source of the incident wave impulses, the transducer, where they are translated back into an electrical form, amplified and then analyzed on an oscilloscope and recorded. In this way, the distances between major points of change of velocity (*i.e.*, areas of discrete differences in density of adjacent tissues) of the wave motion can be measured if these points are all close to perpendicular to the direction of incident wave motion. In this article, then, the record shows major oscillations at the transducer site, the anterior wall of the ventricle, the posterior wall of the ventricle and, in cases of erroneous alignment of the transducer, at the mitral valve, the descending aorta and thoracic spine. These errors can be recognized by the unusual distance of these oscillatory sites from the transducer on the oscillographic record.

In the case of a patient whose pericardial sac con-

tains a normal amount of fluid, the fluid column is so narrow that the echo signifying change in velocity of the transmitted wave impulse is not strong enough to record on the oscilloscope. However, in a patient who has a significant increase over normal of pericardial fluid, such as one with pericardial effusion, an oscillation at the posterior myocardium pericardial fluid interface is seen, followed by an interval of relative quiet as the transmitted wave passes through the pericardial effusion and then another strong oscillation is noted as the wave passes from fluid to aerated lung with a resultant high amplitude echo. The result is that there is one oscillation band in the normal case, whereas in the case of pericardial effusion there are two oscillation bands.

Using this method, the authors performed 84 studies on 55 patients and found 29 positive for pericardial effusions. These 29 positive studies were found in 17 patients. Of these 17 patients, pericardial effusion was confirmed by intravenous CO_2 study in 13. Three of the 4 remaining had negative CO_2 studies but 1 of these had a traumatic pericarditis by clinical parameters. The other 2 were false positives on echocardiography due to faulty technique. One patient was too ill to undergo CO_2 studies but clinically had pericardial effusion. There were no proved false negatives. Correlation of the volume of pericardial effusion between the two methods of diagnosis used was poor and several possible explanations for this are offered.—*Victor Brasseur, M.D.*

Kelley, Maurice L., Jr., and Frazer, John P. Symptomatic mid-esophageal webs. *J.A.M.A.*, July 11, 1966, *197*, 143–146. (From: Departments of Medicine and Surgery, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.)

The authors report a patient with mid-esophageal webs, discuss the appropriate management and give comments on esophageal webs.

Their case was a 46 year old man who experienced intermittent delay of solid food in the esophagus of a progressive nature for a period of 20 years. Dysphagia was secondary to several membrane-like constrictions in the mid-esophagus. The margins of the defects were smooth and the adjacent esophagus appeared flexible at fluoroscopy. A small, sliding hiatal hernia and lower esophageal ring were also present but did not contribute to the symptoms. There was no evidence of an underlying motility disturbance. The webs were successfully treated by dilatation, initially by direct vision and later by blind bougienage.

The symptom-producing webs are divided into those of the upper, middle, and lower esophagus.

1. The upper esophageal webs are usually found just inferior to the cricopharyngeus. They emanate from the posterior wall, produce an eccentric defect in the lumen, and are allegedly congenital in origin or associated with an iron deficiency anemia (Plummer-Vinson syndrome).
2. Webs of the mid-esophagus are the least common variety about which very little information is available.
3. Lower esophageal webs are seen as a thin ring of restricted distensibility during barium roentgen examination of the esophagus, but no web is visualized at endoscopy in most instances. The authors state that these webs are proximal to the gastroesophageal sphincter and cannot be accepted by themselves as direct evidence of hiatal hernia. Lower esophageal webs may be congenital or inflammatory in origin, while a few are associated with pemphigus.

The presence of several rings in the esophagus suggests a congenital origin. An alternative and equally speculative etiologic theory is that plication and infolding of the mucous membrane occurred secondary to mucosal redundancy developing with sliding at the hiatus and shortening of the esophageal musculature.

According to Schatzki, it is unusual for a ring wider than 20 mm. in diameter to cause repeated episodes of dysphagia.

Only 2 webs were reported in the mid-esophagus out of a group of 58 cases of esophageal webs. One patient was a 72 year old female with dysphagia of 6 years' duration, and the other was a 38 year old man who also had a lower esophageal ring.

The authors feel that the treatment of choice for symptomatic esophageal web is dilatation. Two patients with mid-esophageal webs encountered by Shamma'a and Benedict were also successfully treated by nonsurgical divulsion.—*A. D. Belcher, M.D.*

Abdomen

Ellegast, H. Langzeitbeobachtungen bei der Crohnschen Erkrankung. (Long term observations of Crohn's disease.) *Radiologia Austriaca*, 1966, *16*, 111–125. (Address: I. Medizinische Universitätsklinik, Spitalgasse 23, Wien IX, Austria.)

Of 20 cases reported, 11 were histologically verified after surgery. In 10 patients, the disease was chiefly confined to the terminal ileum; 4 of 10 patients also had other intestinal foci, such as in the cecum, descending colon, other small bowel segments, and the stomach; in one patient only the jejunum was involved; in another, the onset was in the stomach. A roentgenographic diagnosis of Crohn's disease was made in 6 cases. The remaining 3 patients probably represented examples of nonsclerosing ileitis.

More than half of the 20 patients were observed over a 10-year period and 2 cases were followed more than 30 years. Recurrences were found in the anastomotic loop in 4 instances and an associated fistula

was found in 2 cases. Three patients died of the disease, one only after 3 years from onset of illness.—*J. Zausner, M.D.*

MARTIN, ET., CORCOS, V., and ALBANO, O. (Paris and Bari). La dilatation congénitale des voies biliaires intrahépatiques segmentaires (maladie de J. Caroli). (Congenital dilatation of segmental intrahepatic biliary pathways [J. Caroli's disease].) *Presse méd.*, Oct., 1965, *73*, 2565–2570.

This disease, of congenital origin, was first described by J. Caroli in 1958. It is an entity with clinical symptoms of repeated pain in the hepatic region, slight fever, and absence of jaundice or portal hypertension.

In the case reported these symptoms were observed since infancy, however without handicapping the growth of the patient.

The roentgen signs were segmental dilatation of intrahepatic biliary pathways with numerous calculi being formed within the dilated ducts (as demonstrated by postoperative cholangiography). Precalyceal renal canalicular dilatation within the pyramids was also observed. The condition probably represents a recessive hereditary trait.

The differential diagnosis from congenital polycystic liver and from congenital fibrosis of the liver is discussed.—*Jirair N. Sarian, M.D.*

HOGARTH, JEAN, and LAIRD, R. C. Congenital cystic malformation of the bile ducts: report of a case and review of related literature. *Canad. M. A. J.*, July 9, 1966, *95*, 57–61. (From: Departments of Medicine and Surgery, Toronto Western Hospital, and University of Toronto, Toronto, Ontario, Canada.)

Few physicians need to be reminded of the consequences of congenital atresia of the bile ducts with its jaundice in early life and often fatal outcome. The authors call attention to the less dramatic, but equally important, congenital cystic dilatation of the bile ducts by contributing a case of their own in addition to reviewing the literature on this subject. This rare condition is being recognized preoperatively with greater frequency by means of intravenous cholangiography.

The choledochal cyst is most commonly single and localized in the common duct, although the cystic or hepatic ducts may be involved. It tends to occur in females and the vast majority are discovered prior to age of 20 years. The symptoms of pain, jaundice, nausea, and vomiting are nonspecific, but the finding of an abdominal tumor, if present, can point to the diagnosis. Often there is a history of intermittent symptoms. Intravenous cholangiography confirms the suspicion. Unfortunately, oral cholecystography often fails to concentrate in the cystic dilatation.

The authors caution that other factors such as previous surgery and biliary tract disease must be ruled out in order to establish the cyst as congenital in origin. Surgical treatment has included many approaches ranging from excision with plastic repair of the duct to bypass procedures.

The authors' case was a 22 old female with cysts of the common duct and left hepatic duct diagnosed by cholangiography and treated successfully with choledochoduodenostomy.—*James T. Telle, M.D.*

MESTEL, A. L., TRUSLER, G. A., HUMPHREYS, R. P., and SIMPSON, J. S. Pneumoperitoneum in the newborn. *Canad. M. A. J.*, July 30, 1966, *95*, 201–204. (From: Department of Surgery, The Hospital for Sick Children, Toronto, Ontario, Canada.)

This report covers the history of 32 infants in the first 2 weeks of life who showed roentgenologic evidence of free air in the peritoneal cavity. Perforations were found at all levels of the gastrointestinal tract. The over-all mortality rate was 59 per cent. The most common occurrence was in the stomach in which it occurred in 11 children. Other sites included the duodenum, small bowel, Meckel's diverticulum, and large bowel. There were 2 infants in the series in whom exploratory laparotomy disclosed no cause nor perforation. A review of the diagnosis includes: (1) outlining the falciform ligament, (2) the football sign, and (3) the saddle bag appearance.

Under treatment it is emphasized that the child's condition is critical and that every effort has to be made to relieve abdominal distention. Because of the tremendous amount of air in the peritoneal cavity, emergency paracentesis with a needle and syringe should be done before a laparotomy to relieve respiratory distress. A nasogastric tube placed into the stomach would also help. This should be followed by surgery as soon as the condition of the patient will permit.—*David C. Alftine, M.D.*

GYNECOLOGY AND OBSTETRICS

GOLDBERG, BARRY B., ISARD, HAROLD J., GERSHON-COHEN, J., and OSTRUM, BERNARD J. Ultrasonic fetal cephalometry. *Radiology*, Aug., 1966, *87*, 328–332. (From: Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pa.)

The biparietal diameter of the intrauterine fetal head can be determined with a high degree of accuracy with the use of ultrasonic wave impulses. The method consists of applying an ultrasonic wave transducer to the maternal abdomen at a point which causes the impulses, in their passage through the tissues, to strike the nearly parallel parietal areas of the fetal cranial vault at near right angles so that the resultant reflected waves return to the trans-

ducer at high and about equal amplitude. It is then possible to measure the distance between the echoes on a precalibrated oscilloscope.

The authors compared the oscillographic measurements prior to delivery with caliper measurements after delivery in 75 cases and found an average variation of 1.4 mm. with no single difference greater than 4 mm.

Several useful clinical applications for ultrasonic fetal cephalometry were studied:

(a) *Cephalopelvic Relationships.* The interspinous diameter of the maternal pelvis obtained by x-ray pelvimetry was compared with the biparietal diameter of the fetal head obtained with the ultrasonic method in 11 cases of breech presentation. In 3 of these cases the fetal biparietal diameter was found to be larger than the interspinous diameter and these were then delivered by cesarean sections. The others delivered normally with the exception of one found to have a prolapsed cord. Six cases of vertex presentation were found to have cephalopelvic disproportion by this method and cesarean section was proved necessary after trials of labor. The authors found such a high degree of accuracy in their predictions of cephalopelvic relationships that they were encouraged to delete previously routine lateral pelvic views, thus reducing x-ray exposure.

(b) *Growth of Fetal Head.* A linear increase in fetal biparietal diameter of 1–2 mm. per week is expected in the last trimester. Arrest in this size increase is presumptive evidence of placental insufficiency. On the other hand, a decrease in the diameter over a one week interval suggests fetal death, especially when fetal heart tones cannot be heard.

(c) *Fetal Weight.* The authors plotted the average biparietal diameter after birth against the birth weights in about 300 infants in graph form and were thus able to predict fetal weights within 8 oz. in over 80 per cent of cases. An accurate knowledge of fetal weight is of considerable importance in cases in which it is deemed necessary to terminate gestation early to avoid late gestational complications—for example, in the diabetic or toxemic patient.

(d) *Localization of Fetal Head.* This is useful in cases of maternal obesity, when the fetal head cannot be palpated.—*Victor Brasseur, M.D.*

Genitourinary System

Henson, Paul E., Jr., and Boyarsky, Saul. Constant infusion excretory urography. *J. Urol.*, June, 1966, *95*, 814–817. (From: Division of Urologic Surgery, Duke University Medical Center, Durham, N. C.)

This technique is employed in those patients who have poor renal function, when conventional excretory urography has not produced satisfactory or adequate information, and in any instance where retrograde pyelography is contraindicated.

The patients are prepared as for routine excretory urography and tested for sensitivity to the radiopaque material prior to injection. A survey roentgenogram is made, then 150 cc. of 50 per cent hypaque with a similar volume of 5 per cent dextrose and water is injected intravenously in 3 to 5 minutes through an 18 gauge needle. Roentgenograms are taken at 2, 10 and 20 minute intervals and subsequently as indicated.

No untoward side reactions were experienced, and there has been no significant effect upon the urea excretion following this method of urography. The pyelograms obtained with the infusion technique in the selected group of individuals show a distinct advantage over those obtained by the routine procedure. In addition to the clinical value, this procedure also has been found useful in conjunction with cinefluorography in the laboratory. The authors illustrate the findings with 4 composite figures.

In summary, constant infusion excretory urography is safe, convenient and readily performed. When indicated, it has provided better visualization of the pathologic anatomy of the urinary tract and more information than conventional urography. It has obviated the use of retrograde pyelography in a significant number of instances. It has allowed adequate visualization of the urinary tract in patients with azotemia.

The side reactions are not significantly different from those observed with conventional intravenous urography.—*George W. Chamberlin, M.D.*

Schencker, Bernard. Further experience with drip infusion pyelography. *Radiology*, Aug., 1966, *87*, 304–308. (From: Department of Radiology, U. S. Army Hospital, Fort Jackson, S. C.)

The author reports on his experience with more than 1,000 drip infusion pyelographic studies. This experience has confirmed the simplicity, safety, reliability, and over-all excellence of this technique in which 250 cc. of 25 per cent hypaque or 30 per cent renografin are administered by rapid intravenous drip infusion. When dehydration prior to the examination is obtained, this amount of the contrast medium has been found to be an adequate minimal adult dose. The excellence of this technique is felt to depend upon diuresis and complete filling of the urinary tract induced primarily by the osmotic diuretic effect of the large amount of contrast material used.

High-quality pyelograms, nephrotomograms, and voiding cystourethrograms were obtained and the method proved of special worth in evaluating the ureters and in screening hypertensive patients for renovascular disease. In addition, satisfactory pyelograms were obtained in many patients with elevated blood urea nitrogen levels. The need for retrograde pyelography with its attendant risks was

greatly reduced. Not a single serious reaction was encountered, and minor side-reactions showed no increase in incidence over standard low-dose pyelography.—*Donald N. Dysart, M.D.*

MORGAN, CECIL, JR., and HAMMACK, WILLIAM J. Intravenous urography in multiple myeloma. *New England J. Med.*, July 14, 1966, *275*, 77–79. (From: Department of Surgery, Division of Urology, and the Department of Medicine, Division of Hematology, University of Alabama Medical Center, and Veterans Administration Hospital, Birmingham, Ala).

A current trend, based on recent publications has been to refrain from performing intravenous urography on patients with multiple myeloma. Acute renal failure in myelomatous patients is due to the intratubular aggregation and precipitation of Bence-Jones proteins. Various authors have contended that contrast material used in intravenous urography facilitates precipitation of the Bence-Jones proteins.

The authors used the presence of oliguria and/or significantly increased creatinine or blood urea nitrogen as criteria for acute renal failure. From 480 patients with well-documented multiple myeloma, 123 who had undergone intravenous urography were selected, and their histories were evaluated using this standard for acute renal failure. They found that none of the 123 patients had developed acute renal failure following the procedure.

When acute renal failure does occur in myelomatous patients, it is more likely that it is the result of dehydration and aciduria. Contrast infusion nephropyelography which does not require dehydration is the technique of choice in these patients. In addition, for those exhibiting chronic renal disease with elevated serum uric acid, the use of alkalinizing agents in recommended.

Emphasis is placed on performing intravenous urography only on myelomatous patients who have definite indications for such a study.—*John A. Knote, M.D.*

SMITH, ARTHUR M. Comparison of standard and cine cystography for detecting vesicoureteral reflux. *J. Urol.*, July, 1966, *96*, 49–50. (From: Department of Surgery [Urology], Cornell University Medical College, and the Department of Surgery [Urology], James Buchanan Brady Foundation, of the New York Hospital, New York, N. Y.)

The author studied 145 patients, most of whom were under 14 years of age, with the purpose of evaluating and comparing vesicoureteral reflux by standard spot film radiographic technique *versus* cineradiography. Each patient underwent both examinations and all studies were performed within a few days of each other with no surgical or other therapeutic measures intervening.

Reflux was demonstrated in 45 of 145 patients by either one or both methods. Thirty-four, or 76 per cent, of all cases were revealed by the standard cystographic method and serial radiography. The cineradiographic technique alone showed vesicoureteral reflux in 36 cases, or 80 per cent.

In a further breakdown of the data, the author divided the patients into 3 groups: *Group A* were those who had reflux proven by cineradiography alone and were negative by the standard cystographic technique. In this group there were 11 patients, or 24 per cent of the total number of 45. In *Group B*, 25 of the 45 showed vesicoureteral reflux by both cine and standard techniques. *Group C* consisted of 9 patients who showed reflux by standard cystography alone and were negative by the cineradiographic technique.

From the above information, it is obvious that neither method alone revealed all of the cases of reflux and there was very little difference between the standard technique and the more expensive cineradiography.

The author is impressed with the relative efficiency of the standard cystographic methods particularly for those urologists who see only an occasional patient in whom reflux is suspected. The effectiveness of standard cystography appears to be adequate, particularly if its limitations are recognized. Cineradiography on the other hand is desirable in those institutions where a large number of patients are examined and whenever study of the physiology of voiding is indicated.—*George W. Chamberlin, M.D.*

BABANOURY, AGHA B., and BOGGS, LAWRENCE K. Miliary tuberculosis following retrograde pyelogram. *J. Urol.*, July, 1966, *96*, 101–102. (From: Charlotte Memorial Hospital, Charlotte, N. C.)

This is a single case report of a patient with an unrecognized tuberculous infection of the left urinary tract. Following retrograde pyelography, the patient developed persistent fever and miliary lesions in the lungs. After considerable time interval, a sputum examination revealed tubercle bacilli and subsequent follow-up examination following a left nephrectomy showed a large cavity in the upper pole of the left kidney. The patient was successfully treated with antituberculous chemotherapy.

The left retrograde pyelograms showed pyelovenous backflow, and it is assumed that the trauma associated with the left retrograde pyelography resulted in dissemination of tubercle bacilli by way of the renal veins.—*George W. Chamberlin, M.D.*

RIESER, CHARLES, and DEITCH, MILTON J. Value of renal angiography in everyday

urologic practice. *J. Urol.*, July, 1966, *96*, 24–30. (From: Emory University Hospital and the Grady Memorial Hospital, Atlanta, Ga.)

The authors of this article have reviewed records of 226 patients who have had renal angiography for diagnosis. They conclude the following:

In the area of renal infection, renal arteriography will occasionally show compression or obstruction of the excretory passages by a blood vessel. An occasional case of segmental chronic pyelonephritis may be evaluated for segmental resection by the use of renal arteriography. Renal trauma may be demonstrated satisfactorily by arteriography. The extent of the parenchymal disruption and presence of extravasation or of renal infarction may be demonstrated by this method. In instances of suspected mass lesions of the kidney which are difficult to diagnose by the routine pyelographic procedure, angiography is indicated prior to surgery.

Of the 226 patients discussed in this paper, 6 had complications. Three of these were due to hemorrhages from the site of the femoral artery puncture; 1 was a thrombosed femoral artery; 1 was caused by a broken spring guide during the procedure; and in 1 instance the spring guide required open surgery for extraction. There were no deaths, neurologic complications or loss of extremities associated with this series of patients.

The authors illustrate the value of renal angiography by 11 composite figures.—*George W. Chamberlin, M.D.*

Burke, Gerald, Halko, Arlene, and Coe, Fredric L. Dynamic clinical studies with radioisotopes and the scintillation camera: I. Sodium iodohippurate I 131 renography. *J.A.M.A.*, July 4, 1966, *197*, 15–24. (From: Radioisotope Laboratory, Department of Metabolism and Endocrinology, Division of Medicine, Michael Reese Hospital and Medical Center, Chicago, Ill.)

An excellent review of the theoretic aspects of dynamic studies with radioisotopes and the instrumentation needed to carry these studies out is presented. The scintillation camera of Anger is described and its ability to fulfill the need in dynamic studies is discussed.

The renogram curve is analyzed and the physiologic kinetics that are responsible for the various segments of the curve are reviewed. The mean renal transport time of iodohippurate is dealt with and at least three intrarenal mechanisms are discussed that can affect the transit time. These are alteration of the flow and/or volume of the intrarenal urine and changes in the rate at which iodohippurate traverses the cells and interstitial spaces of the kidneys. Various altered states that could be related to the above mechanisms are presented and the desirability of a system that would permit constant visual monitoring of iodohippurate I^{131} passage at the same time that the renogram curve is inscribed to permit more precise interpretation of the renogram is suggested.

A method of constant visual monitoring of iodohippurate I^{131} passage through the renal parenchyma and pelvis at the time the renogram curve is inscribed is presented.

Conditions studied, using this method, were: (1) normal renal function under ambient hydration; (2) effects of water diuresis; (3) dehydration; (4) acute glomerulonephritis; and (5) severe impairment of renal function.

The results, in a graphic form, and the alterations of the renogram curve are well depicted.

The method is rather time consuming and subject to error from movement, but a modification is proposed that would reduce this error.—*Richard T. Browne, M.D.*

Pearlman, Carl K. Cystitis due to cytoxan: case report. *J. Urol.*, May, 1966, *95*, 713–715. (Address: 1518 N. Sycamore Street, Santa Ana, Calif.)

This article consists of a single case report of a 20 year old patient with Hodgkin's disease treated by cytoxan with resulting severe cystitis proven by biopsy and by pathologic examination at autopsy.

Cytoxan or cyclophosphamide is a cytotoxic agent used in the treatment of some forms of malignant disease. In animals it can regularly induce bladder damage consisting of ulceration of the mucosal epithelium, hemorrhage, edema, and necrosis in smooth muscle and small arteries. This bladder damage in animals could be prevented by promoting brisk diuresis during the first few hours after administration of the cytoxan. In a series of 59 children treated with this drug, urinary frequency, dysuria or hematuria occurred in 20 patients who received the drug for more than 2 weeks. Cystoscopic examination revealed hemorrhages and ulcerative lesions in the mucosa of the bladder. In children with severe involvement, bladder contracture occurred. In others with less marked bladder involvement, the lesions tended to heal in time with the formation of considerable scar tissue.

This article includes 1 illustration of the excretory urogram showing the bladder deformity, and 1 showing the histologic nature of the bladder lesions.—*George W. Chamberlin, M.D.*

Skeletal System

Collesson, L., Grilliat, J.-P., Mathieu, J., and Laurent, J. L'ostéose raréfiante dans les cirrhoses du foie. (Rarefying osteoporosis in cirrhosis of the liver.) *Presse méd.*, Oct.,

1965, *73*, 2571–2574. (From: Service de Médecine D, Centre hospitalier régional F 54-Nancy, France.)

This study is based upon 60 cases of cirrhosis of the liver, of which 44 had satisfactory roentgenograms for interpretation. The following findings were noted: 16 patients exhibited osteomalacia; another 16 patients presented a mixture of osteomalacia and osteoporosis; 6 showed osteoporosis; and in 6 the roentgenograms of the pelvis and of the dorso-lumbar spine were normal.

These results were obtained before the patients were treated with corticosteroids; hence, fewer cases of osteoporosis were observed as compared to other authors. However, osteomalacia is an osteoporotic condition, and added to the mixed and simple cases of osteoporosis, there is almost always rarefaction of bone demonstrable in cirrhotic patients.

The findings were also verified by calcium studies which invariably showed hypocalcemia, more pronounced in ascitic patients.

The main causes of the osteoporosis are: impaired calcium and vitamin D absorption, protein deficiency and particularly renal deficiency. The alkaline phosphatase is elevated and the serum phosphorus is usually normal.—*Jirair N. Sarian, M.D.*

Christiaens, L., Deminatti, M., Walbaum, R., and Debeugny, P. A propos d'une famille atteinte de brachydactylie héréditaire type Vidal. (Report of a family afflicted with hereditary brachydactylia of Vidal type.) *Lille méd.*, Sept.-Oct., 1965, *10*, 686–691. (From: Service de Pédiatrie du C. H. U. de Lille, Lille, France.)

The authors report the case of a 5 year old girl afflicted with hereditary type of brachydactylia (mother and one brother showing the same digital anomaly). In addition she has other abnormalities such as ptosis of one eyelid, somewhat deformed thorax and in particular club feet and oligophrenia (I.Q. below 50).

Roentgenographic reproductions of both hands, genealogic and chromosomal studies, and several tables are included.—*Jirair N. Sarian, M.D.*

Ambrose, George B., Alpert, Meyer, and Neer, Charles S. Vertebral osteomyelitis: a diagnostic problem. *J.A.M.A.*, Aug. 22, 1966, *197*, 619–622. (From: Departments of Radiology and Orthopedic Surgery, College of Physicians and Surgeons, Columbia University, and Columbia-Presbyterian Medical Center, New York, N. Y.)

In a series of 24 patients with proven hematogenous pyogenic vertebral osteomyelitis, the disease was insidious in onset.

The roentgenographic findings are inconclusive so that vertebral body biopsy for blood culture proof is required for treatment.

The summary of the 24 cases is given in a table including all pertinent data. Treatment is also covered.

The presentation is a short, concise, review of this rather subtle and sometimes elusive disease.—*David C. Alftine, M.D.*

Lam, S. F., and Hodgson, A. R. Non-spinal pyogenic psoas abscess. *J. Bone & Joint Surg.*, July, 1966, *48-A*, 867–877. (From: Queen Elizabeth and Queen Mary Hospitals, Hong Kong, Hong Kong.)

This report covers the details of 24 cases of proven primary isolated abscess in the psoas sheath as a definite clinical entity. The organism responsible in the majority of patients was *Staphylococcus pyogenes*. The authors drew this information during the course of treatment of tuberculous psoas abscesses.

Their findings substantiate the fact that this non-spinal pyogenic psoas abscess is not due to tuberculosis and they stress that this entity has not been given enough attention in the past.

Very thorough and painstaking recording of the several case histories is included. The diagnoses are also well tabulated.

The roentgenographic findings are negative with respect to the bones of the thoracolumbar spine, pelvis, and both hip joints. Usually it is possible to detect a prominence or bulging of the psoas shadow when the abscess is large.

Treatment includes both surgery and antibiotic therapy.—*David C. Alftine, M.D.*

SKULL RADIOGRAPHY
A Simplified System

JOSEPH SELMAN, M.D.
Clinical Assistant Professor of Radiology
University of Texas
Southwestern Medical School
Tyler, Texas

The most comprehensive manual devoted entirely to radiography of the skull and its contents and the facial bones. Data are limited to the most useful and practical aspects of radiography of the mature skull.

Partial list of Contents includes:

- *Radiography of the Skull as a Whole*
- *Radiography of the skull—Emergency Survey*
- *Pneumoencephalography*
- *Cerebral Angiography*
- *Mastoid and Petrous Portions of Temporal Bones*
- *Temporomandibular Joints*

The literature has been culled and combined with the author's experience, and the resulting radiographic projections standardized to facilitate accurate positioning. The descriptions have purposely been made concise, though detailed, and illustrations of both the position of the head and the appearance of the resulting radiograph have been included.

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MEDICAL RADIOGRAPHIC TECHNIC (3rd Ed., 2nd Ptg.). *Rewritten by* **William L. Bloom, Jr., John L. Hollenbach,** *and* **James A. Morgan,** *all of the Technical Service X-Ray Dept., General Electric Company, Milwaukee. Originally under the editorial supervision of* **Glenn W. Files (1897-1945).** Jan. '67, 368 pp. (7 × 10), 510 il., 7 tables, $11.00

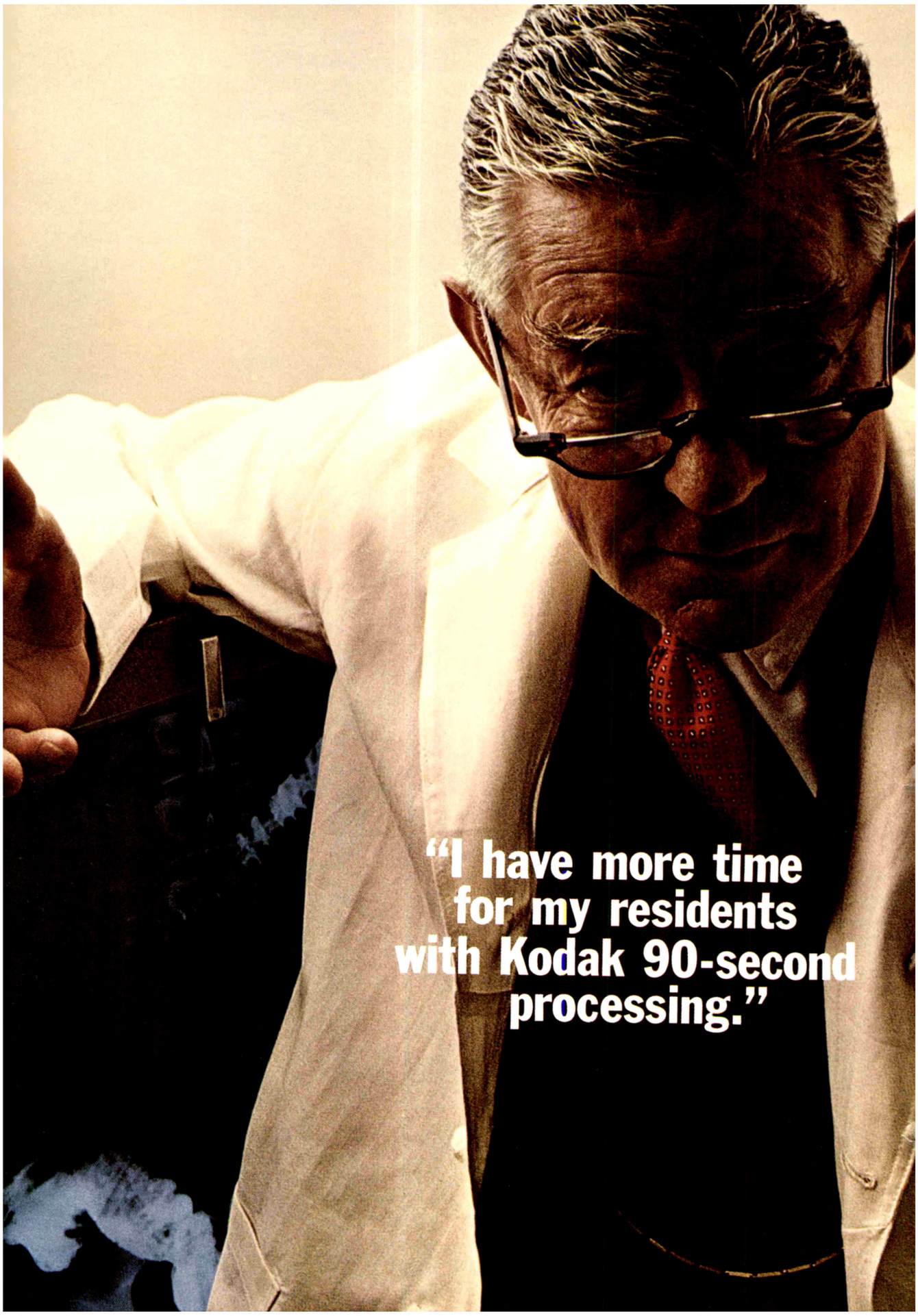
THE COMMON BILE DUCT: Operative Cholangiography, Biliary Endoscopy and Choledocholithotomy *by* **Clarence J. Schein, Wilhelm Z. Stern,** *and* **Harold G. Jacobson.** *All of Montefiore Hospital and Medical Center, New York City.* Oct. '66, 304 pp. (8½ × 11), 386 il. (16 in color), (Amer. Lec. Roentgen Diagnosis edited by Lewis E. Etter), $22.50

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INTRODUCTION TO SHORTWAVE AND MICROWAVE THERAPY (3rd Ed.) *by* **Harald Thom,** *Orthopädische Universitatsklinik, Heidelberg, Germany.* July '66, 184 pp. (6¾ × 9¾), 167 il., $11.75

CLINICAL RADIOISOTOPE SCANNING *by* **Yen Wang,** *University of Pittsburgh, Pa.* March '67, about 336 pp. (6¾ × 9¾), about 280 il., 8 tables, (Amer. Lec. Roentgen Diagnosis).

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same day re-examination in oral cholecystography

obviously practical, but... diagnostically valuable?

UNSATISFACTORY opacification after routine cholecystography doesn't necessarily mean the gallbladder is diseased. Poor absorption of the contrast agent from the gastrointestinal tract, or the inability of the liver to conjugate and excrete it, might just as well be the cause.[1]

'Nonopacification' is not a condition you can treat

To determine the cause of nonopacification, most physicians request re-examination. There are two ways this has been done by the oral route in the past:

- by starting all over again at a later date — and sometimes doubling the dose of contrast agent on the second try;
- by administering more contrast agent the evening of the first unsuccessful examination (and, again, sometimes doubling the dose) and repeating the study the following day.

Both these methods share two inherent disadvantages. They take a good deal of time, and they require the patient to take a good deal of oral contrast agent. The amount given assumes clinical importance because it has been reported higher doses may result in considerable patient discomfort because of diarrhea and other significant side effects.[1]

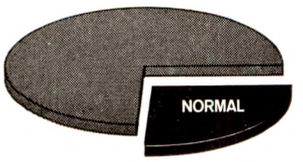
Recently it's been demonstrated, however, that the use of Oragrafin Calcium (Squibb Calcium Ipodate) permits repeat films with significant cuts in both time and total dosage.

Oragrafin Calcium—absorbed so rapidly you can re-examine the same day

"The advantage of the calcium ipodate method is that the examination can be completed in five additional hours with a limited dose of contrast agent."[1]

The method is as productive as it is simple. If the initial opacification is unsatisfactory, the patient is given 3 Gm. of calcium ipodate. Films are repeated 5 hours later. Here are the results of a recently published study on same day re-examination using Oragrafin Calcium:[1]

ANALYSIS OF ORAGRAFIN CALCIUM REENFORCEMENT
IN 76 CASES OF UNSATISFACTORY INITIAL OPACIFICATION



Positive information	24	Normal by present criteria	20
Abnormal gallbladder (by inference)	52	Cholelithiasis	4

Correlation of x-ray findings and surgical data was excellent. Because many patients were elderly or had complications contraindicating it, surgery was performed in only 13 cases, with these results: Stone — 6; Liver metastases — 3; Carcinoma of pancreas — 1; Carcinoma of gallbladder — 1; Cirrhosis — 1; Normal — 1

Had the initial failure of opacification been assumed to be due to gallbladder disease, the 20 patients (26%) found normal by re-examination might have been erroneously diagnosed and might have undergone unnecessary surgery.[1]

"Same day re-enforcement oral cholecystography utilizing calcium ipodate . . . is a rapid, accurate, low-dose method of obtaining additional information about a gallbladder which is unsatisfactorily opacified following routine cholecystography."[1]

There are other advantages to such rapid absorption. Even without prior preparation of the patient, both cholangiography and cholecystography can be performed on the same day. Optimal concentration in the hepatic and biliary ducts usually occurs within 1 to 3 hours. Although the gallbladder is optimally opacified approximately 10 hours after ingestion of Oragrafin, diagnostically valuable information can often be obtained within 5 hours or less.

Dosage and Administration: For oral combined cholangiography and cholecystography: *Same day* — Oragrafin Calcium Granules — 2 packets 1 hour before initiating examination. *Overnight* — Oragrafin Calcium Granules—1 packet or Oragrafin Sodium Capsules (Squibb Sodium Ipodate) —6 capsules 10 to 12 hours before radiography, plus an additional packet of Granules one hour before examination.

Supply: Oragrafin Calcium Granules — single-dose foil packets of 3 Gm. of calcium ipodate granules, providing 61.7% iodine content. Oragrafin Sodium Capsules — 0.5 Gm. sodium ipodate per capsule, providing 61.4% iodine content.

Contraindications: Contraindicated for persons sensitive to oral iodine compounds or for patients with combined renal and hepatic disease or severe kidney impairment. Gastrointestinal disorders (which may result in inadequate biliary secretion of medium) often impair visualization.

Side Effects and Precautions: Both calcium and sodium ipodate are usually well tolerated. Mild and transient nausea, vomiting, or diarrhea sometimes occur; but the incidence can be reduced by using the calcium Granules and restricting the dosage to 3 Gm.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin reactions, and rarely anaphylactoid shock. They are more likely to occur in the individual with a hypersensitivity diathesis. Antihistamines and corticosteroids are used to control these side effects, but the occasional serious anaphylactoid reactions require the immediate use of epinephrine or phenylephrine, oxygen, and intravenous corticosteroids. For full information see Package Insert.

Reference: 1. Crummy, A. B.: Wisconsin M. J.: 65:84, 1966.

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visualization → functioning gallbladder
nonvisualization → gallbladder disease*

Numerous studies with large numbers of patients show a diagnostic accuracy ranging from 95 to 100%

Baker and Hodgson[1] of the Mayo Clinic and Mayo Foundation, reporting on a series of 1,207 cholecystographic examinations with TELEPAQUE in which all diagnoses were subjected to surgical and pathological verification, found 98 per cent of all the diagnoses were correct. *All* the nonvisualized gallbladders were found to be diseased, and the "increased accuracy of this diagnosis seemed to have a direct relationship to the medium employed". (The authors emphasize, however, the primacy of correct technical procedure and vigilance by the radiologist over the particular contrast medium used.)

Alderson[2] found TELEPAQUE 99 per cent accurate in cholecystography of 315 patients. He concluded that "TELEPAQUE is held to be the most satisfactory for routine radiological investigation of gallbladder symptoms". Six other groups of investigators have published similar results with TELEPAQUE which varied in accuracy from 95 to 100 per cent.[3-8]

only with Telepaque is such diagnostic accuracy so substantially documented

References: 1. Baker, H. L., Jr., and Hodgson, J. R. (Mayo Clinic and Mayo Foundation): Further studies on the accuracy of oral cholecystography, *Radiology 74*:239, Feb., 1960. 2. Alderson, D. A. (King's College Hosp., London): The reliability of Telepaque cholecystography, *Brit. J. Surg. 47*:655, May, 1960. 3. Rogers, J. V., Jr., Bonmati, J., Leigh, T. F., and Gay, B. B., Jr. (Emory University Hospital, Atlanta): Correlation of radiographic and surgical findings in gallbladder disease, *J.M.A. Georgia 42*:489, Nov., 1953. 4. Tillinghast, A. J. (New York): X-ray diagnosis in disorders of the biliary tract, *Rev. Gastroenterol. 20*:750, Oct., 1953. 5. Mauthe, H. (St. Agnes Hosp., Fond du Lac, Wis.): The accuracy of X-ray examination of the gallbladder, *Wisconsin M.J. 53*:473, Sept., 1954. 6. Garland, L. H. (San Francisco): New techniques in cholecystography, *Minnesota Med. 39*:433, July, 1956. 7. Whitehouse, W. M. (University Hospital, Ann Arbor, Mich.): Correlation of surgical pathology with Telepaque cholecystography in doses of two grams, *Surg., Gynec. & Obst. 100*:211, Feb. 1955. 8. Dietz, M. W., and Litton, L. D. (Springfield, Mo.): Syllabus of cholecystography, *GP 14*:109, Oct., 1956.

*An extraordinary high degree of accuracy has been achieved with Telepaque in studies involving large series of patients; however, unusual causes of nonvisualization other than gallbladder disease also exist.

Dosage: The TELEPAQUE tablets (0.5 Gm. each) are preferably administered from 10 to 12 hours before the time scheduled for cholecystography. At about 10 P.M., 6 tablets should be swallowed, each with one or two mouthfuls of water (with a total of a full glass of water). In patients where visualization of the extrahepatic ducts is especially indicated, from 10 to 12 tablets have been recommended. In patients with thin or normal build, weighing less than 150 pounds, 4 tablets may prove sufficient.

Side Effects: TELEPAQUE has low toxicity, and side effects when they occur are usually mild. Gastrointestinal effects (diarrhea, cramps, nausea, vomiting) are the most common. Usually the diarrhea is mild, consisting merely of a few loose stools, although in isolated cases it may be severe. Other side effects reported include dysuria, headache and, on rare occasions, skin rash, urticaria, pruritus, and flushing.

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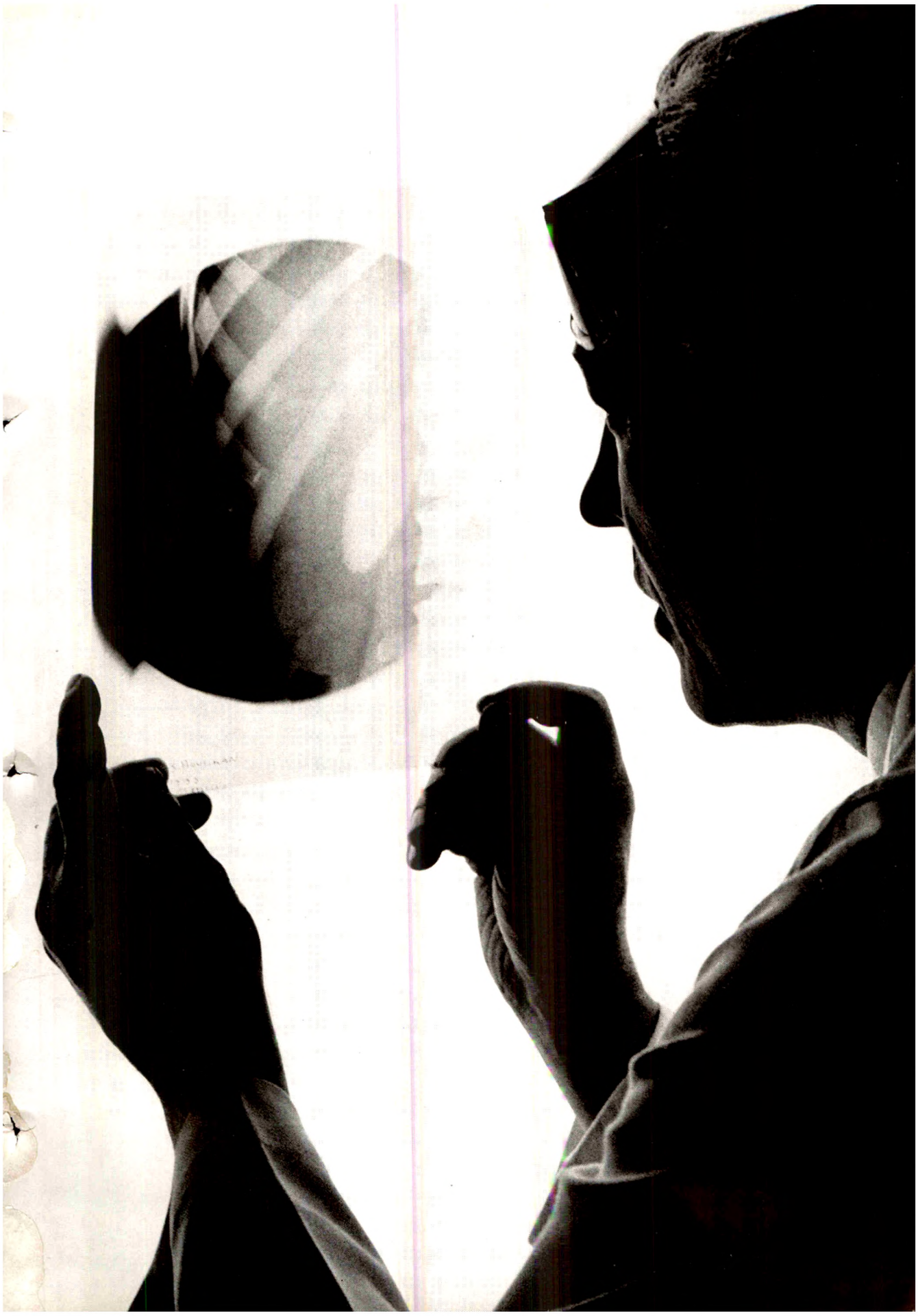
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THE DIAGNOSIS OF HYDATIDIFORM MOLE, MALIGNANT HYDATIDIFORM MOLE AND CHORIOCARCINOMA WITH SPECIAL REFERENCE TO THE DIAGNOSTIC VALUE OF PELVIC ARTERIOGRAPHY *by* **Ulf Borell, Ingmar Fernström, Gunnar Moberger,** *and* **Lars Ohlson,** *all of Karolinska Sjukhuset, Stockholm.* To correlate more closely the findings of gynecologist and radiologist . . . *a systematic description of tumours of the placenta.* Chief emphasis is on the importance of pelvic arteriography in early diagnosis. *Oct. '66, 128 pp. (8½ × 11), 137 il., $9.75*

PRINCIPLES OF RADIOGRAPHIC EXPOSURE AND PROCESSING (2nd Ed., 3rd Ptg.) *by* **Arthur Fuchs,** *Rochester, N.Y.* "This book should be a standard text for all roentgen-ray technicians and a great help to all radiologists who are not familiar with the advantages of the optimum kilovoltage technique . . . a most complete work making available to the radiologist and technician principles and facts needed for the production of consistently high quality roentgenograms."—The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine. *Feb. '66, 300 pp. (7 × 10), 600 il., $10.50*

INTRAVENOUS ABDOMINAL AORTOGRAPHY AND PLACENTOGRAPHY *by* **Melvyn H. Schreiber, Fred J. Wolma,** *and* **Charles K. Hendrick,** *all of the University of Texas, Galveston.* Designed to emphasize the value of a simple, safe, and reliable intravenous means of rendering the abdominal aorta and the placental venous sinusoids opaque. Included in the discussion are comments on indications, selection of patients, necessary materials, reactions and complications, and radiation dosage. *Feb. '67, about 88 pp. (7 × 10), about 66 il. (3 in color).*

LEGAL CONSIDERATIONS ON IONIZING RADIATION: Radionuclides and Radiation Emitting Devices *by* **Gerald L. Hutton,** *U. S. Atomic Energy Commission, Washington.* The author identifies many technolegal problems encountered in the use of radioactive materials and other sources of ionizing radiation and points up a number of considerations which may be involved in avoiding or solving them. Law suits involving X rays and radium are briefly discussed. *Aug. '66, 104 pp., $5.50*

CHEMICAL PROTECTION AGAINST IONIZING RADIATION *by* **Zénon M. Bacq,** *Univ. of Liège, Liège, Belgium. '65, 344 pp., 100 il., 23 tables, (Amer. Lec. Living Chemistry edited by I. Newton Kugelmass), $14.00*

A TEXTBOOK OF ELEMENTARY RADIOGRAPHY FOR STUDENTS AND TECHNICIANS *by* **Donald deForest Bauer,** *Klamath Valley Hospital, Klamath Falls, Oregon. '65, 260 pp., 6 il., 5 tables, $8.50*

RADIOTHERAPY OF BENIGN DISEASE *by* **Stephen B. Dewing,** *Hunterdon Medical Center, Flemington, N. J. With a chapter contributed by* **Ralph Wier Grover,** *Nassau County Tuberculosis Sanatorium, Farmingdale, N. Y. '65, 320 pp., $9.75*

THE PHYSICS OF RADIOLOGY (2nd Ed., 3rd Ptg.) *by* **Harold Elford Johns,** *Univ. of Toronto, Canada.* Includes chapters on diagnostic radiology, isotopes, protection, radiobiology, and rotation therapy. There is detailed discussion of methods by which an x-ray beam can transfer its energy to tissue. *New concepts of energy absorption using the rad are emphasized.* Detailed discussions of supervoltage and teletherapy machines are included. *Sept. '66, 784 pp. (6¾ × 10), 469 il., (Amer. Lec. Radiation Therapy edited by Milton Friedman), $23.00*

RADIOLOGY AS AN ART AND OTHER ESSAYS *by* **John L. McClenahan,** *Hospital of the University of Pennsylvania, Philadelphia.* An x-ray practitioner records his observations about patients, practice, radiologists and himself. Includes personal reminiscences, travel notes, technical suggestions and occasional lines of dissent. The author, concerned about the invisibility of x-ray specialists, is impressed by the opportunities afforded them to observe and assist sick people in a personal way. *Feb. '67, about 156 pp., about 3 il.*

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CLINICAL ROENTGENOLOGY OF COLLAGEN DISEASES *by* **Charles M. Nice, Jr.,** Tulane Univ., New Orleans, La. *Jan. '66, 216 pp., 134 il., (Amer. Lec. Roentgen Diagnosis edited by Lewis E. Etter), $10.75*

AN OUTLINE OF RADIOGRAPHIC FINDINGS IN MULTIPLE-SYSTEM DISEASE *by* **John H. Simonton** *and* **Robert C. Jamison,** *both of Univ. of California at Los Angeles. Jan. '66, 272 pp., $11.75*

THE MEDICAL LEXICOGRAPHER *by* **J. E. Schmidt,** *Charlestown, Ind.* The reader will find scores of new words, etymologic discussions, comparisons and distinctions between words, hundreds of roots and other combining forms, medical abbreviations and contractions, analysis of usage, and important aspects of communication. Includes both a conventional index and a second index of meanings. *Sept. '66, 112 pp. (5½ × 8½), $4.75*

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THE TRAIL OF THE INVISIBLE LIGHT: From X-Strahlen to Radio(bio)logy *by* **E. R. N. Grigg,** *Cook County Hosp., Chicago.* Covers the era of the roentgen pioneers, the golden age of radiology, and the atomic phase. Includes a list of all significant radiologic periodicals, a radio-historic bibliography, a world-wide almanac of x-ray manufacturers, and an abbreviated dictionary of radiologic biography. *'65, 1,016 pp. (8½ × 11), 1,404 figs., (Amer. Lec. Roentgen Diagnosis edited by Lewis E. Etter), $36.75*

THE USE OF DIAGNOSTIC ULTRASOUND IN BRAIN DISORDERS *by* **Charles C. Grossman,** *Presbyterian-University Hospital, Pittsburgh.* Describes in detail the new science of ultrasound diagnosis covering fundamentals of ultrasonics, clinical methodolgy and techniques, determination of normal and displaced brain "midline" by use of the A-scope technique (Sonoencephalography-SEG), etc. *Feb. '66, 172 pp., 146 il., $9.00*

HISTOPLASMOSIS AND NORTH AMERICAN BLASTOMYCOSIS. Radiology and Pathology. An Atlas *by* **Jan Schwarz,** *Jewish Hospital, Cincinnati, and* **Gerald L. Baum,** *V. A. Hospital, Cleveland.* Differential diagnosis is stressed and illustrations relating to other mycoses are found throughout the book. Case sequences demonstrate the variety of roentgenologic patterns that should arouse suspicion of fungal etiology. *May '67, about 320 pp., about 429 il., 5 tables.*

MAMMOGRAPHY *by* **John N. Wolfe,** *Woman's Hospital (Hutzel Hospital), Detroit.* A succinct presentation of the roentgenographic aspects of breast disease. *Stresses a considerable number of roentgen signs of malignancy never previously described.* Correlations between roentgenographic appearance, clinical observation, and pathology are consistent throughout. *April '67, about 320 pp. (8½ × 11), about 191 il., 25 tables.*

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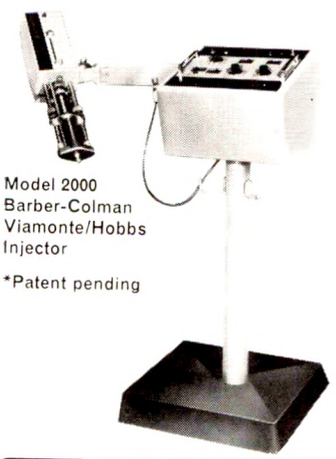
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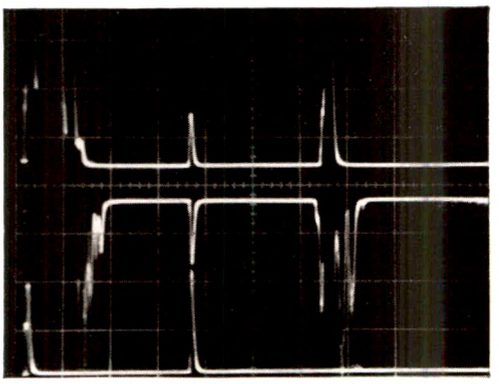
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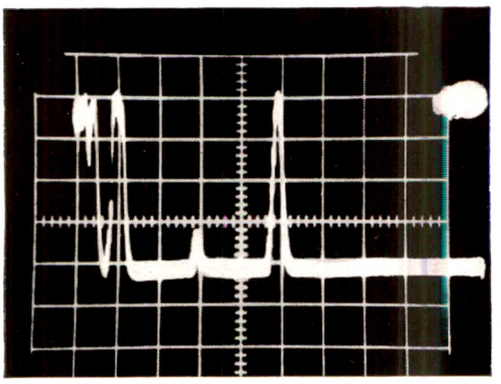
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the diagnostic duality of ultrasound

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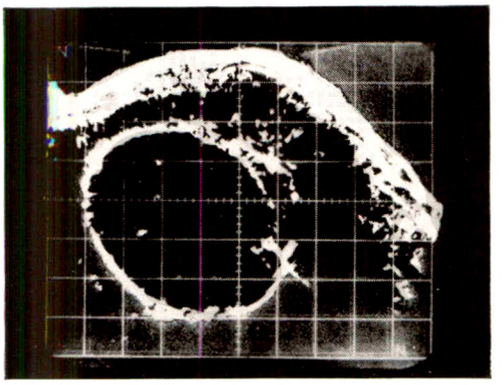


Location of Brain Midline

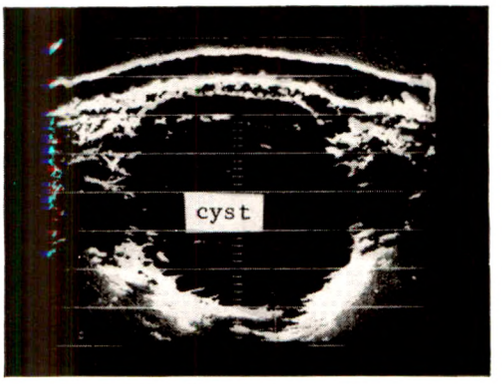


Biparietal diameter of Fetal Head. Ultrasonic measurement was 8.8 cm. Actual diameter at birth two days later was 9.0 cm.

VISUALIZATION
("B" scan)



Sagittal section of Uterus demonstrating Fetal Head.



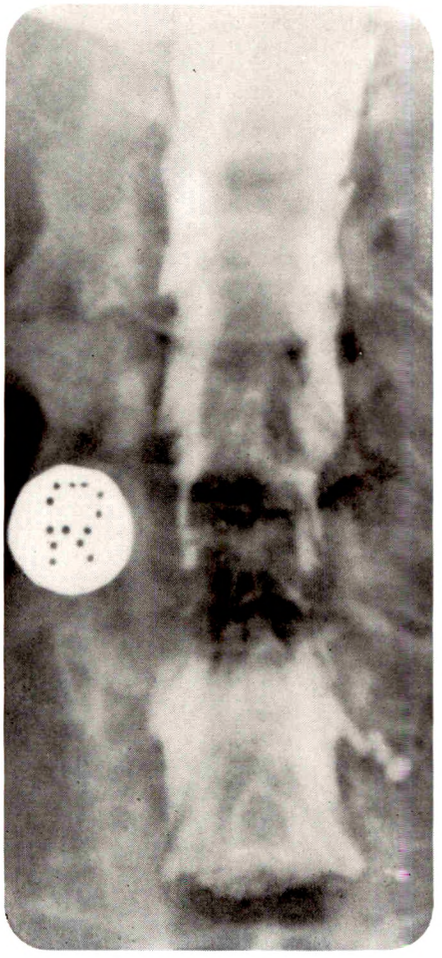
Somagram of malignant Ovarian Cyst.

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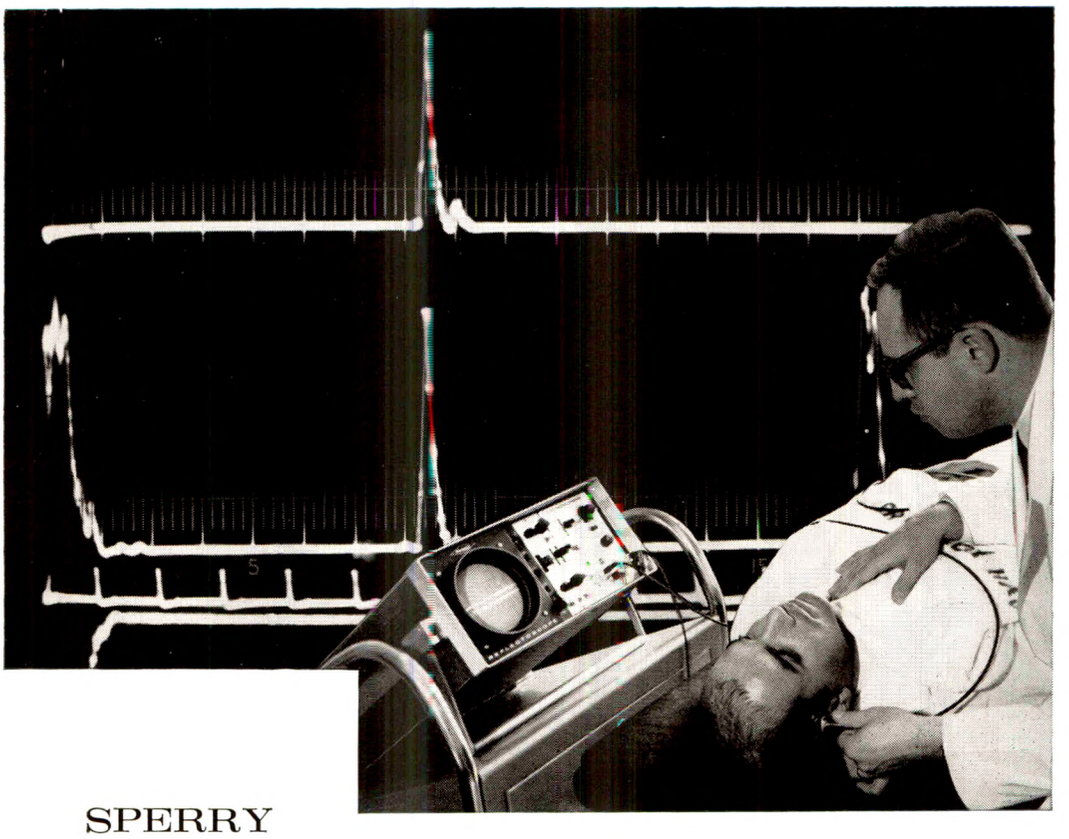
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1. S. Jeppsson, Acta, Chir. Scand 119 (1960) 445-462; Suppl 272(1961)
2. A. Jefferson, Acta Neurochirurgica, x4(1962) 392-409
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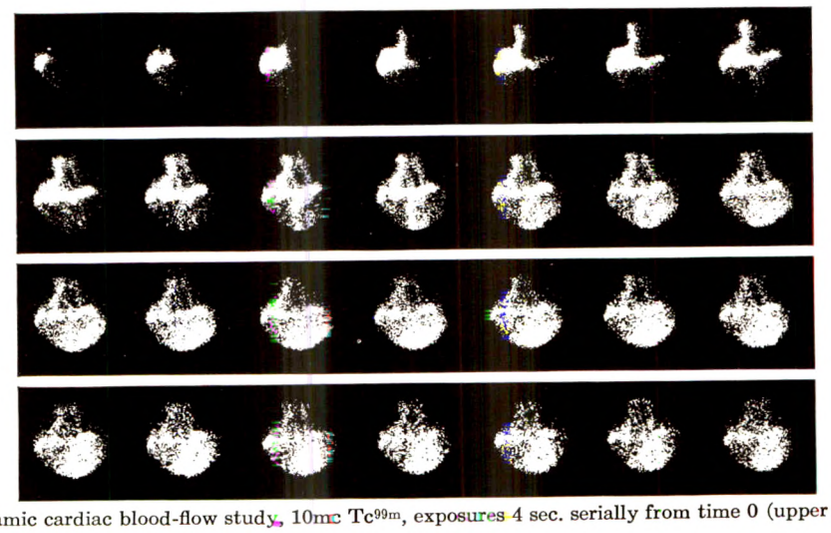
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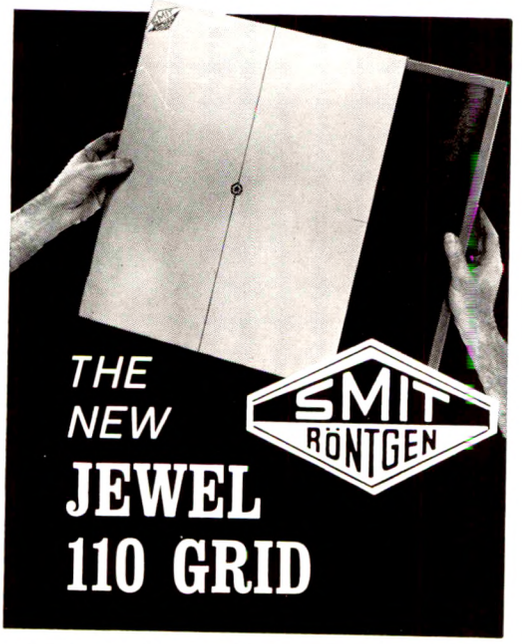
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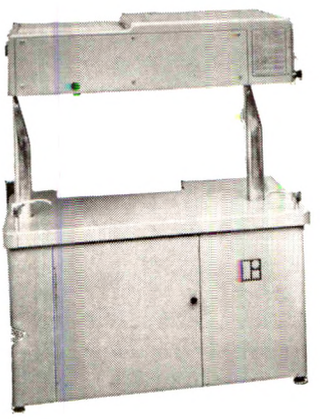
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*Dr. James H. Schulman, patent No. 3,115,578
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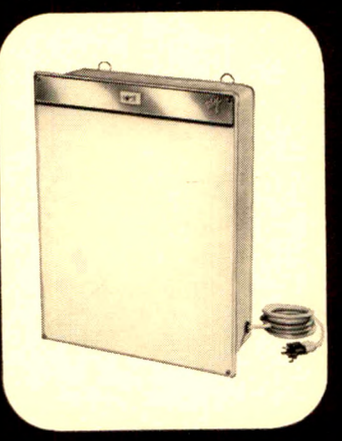
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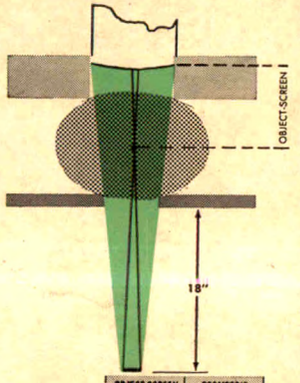
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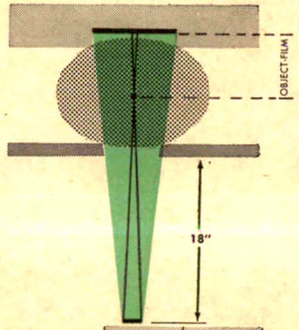
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GALAXY	7.125"	.018"
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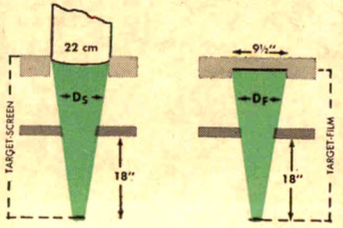
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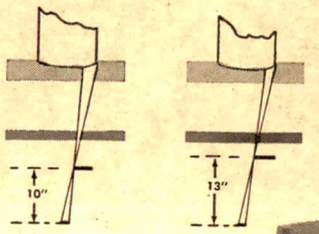
target-screen target-film distances are shorter



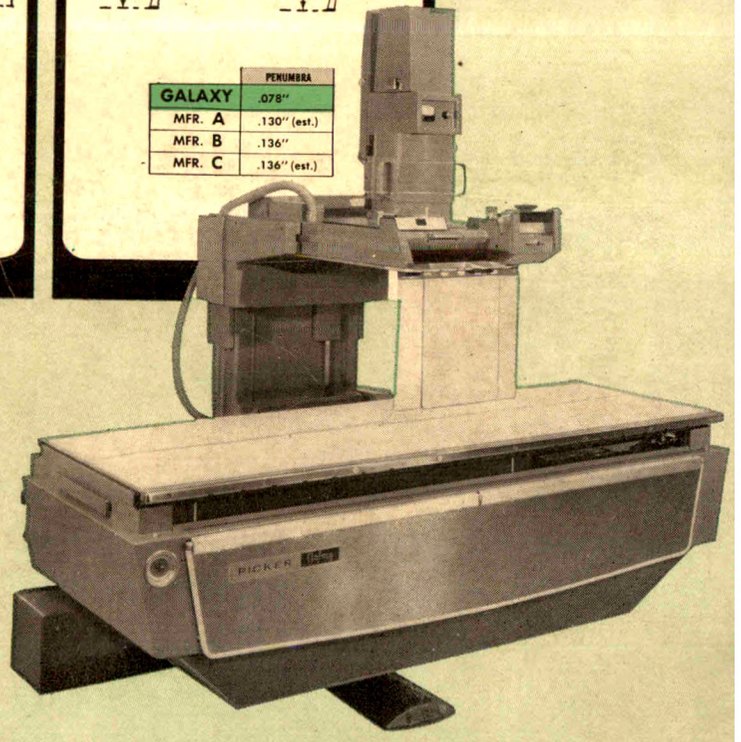
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GALAXY	6.98"	7.48"
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Visualization without radiation through the use of ultrasound.

Not all radiologists have yet caught up with the fact that ultrasonography can supplement, reinforce and sometimes even replace radiography as a diagnostic tool. Impressive clinical evidence has gained for ultrasound the recognition by many that it is a modality they can and should use . . . on a several-times-a-day basis.

For example: the use of a simple echograph to differentiate between cystic and solid masses has been reported. The radiologist, guided by his film, locates the ultrasonic probe over the area in question and makes a simple study of the echoes.

In one study, radiographic evidence of 32 renal masses was refined by the use of ultrasound, which concisely classified 21 cysts, 6 out of 7 tumors, and 4 examples of normal tissue.

Others have compared radiographic and ultrasonic information about the lumen of the aorta and the thickness of its walls. The ability to locate aortic constriction or aneurysm without recourse to x-rays or opaque dyes and to do so quickly and easily can be a welcome supplement to, if not replacement of, more complex radiologic procedures.

Ultrasonic cephalometry has proven so accurate in the measurement of biparietal diameters that in at least one radiology department, the lateral radiograph of the pregnant uterus has been dispensed with. Uterine fibroids have been frequently identified by at least two modes of ultrasonic diagnosis.

The first evidence of mitral stenosis may well be provided by ultrasonic examination. First, or last, however, it is a relatively easy way to study the dynamics of valve action without the use of catheterization or injection technics.

As an alternative to pneumoencephalography in the detection of and followup of shifts in the midline structure, ultrasound in the simple "A"-mode of operation has been widely accepted. Ultrasonic laminography can investigate the possibility that a tumor instead of a subdural hematoma has caused the shift.

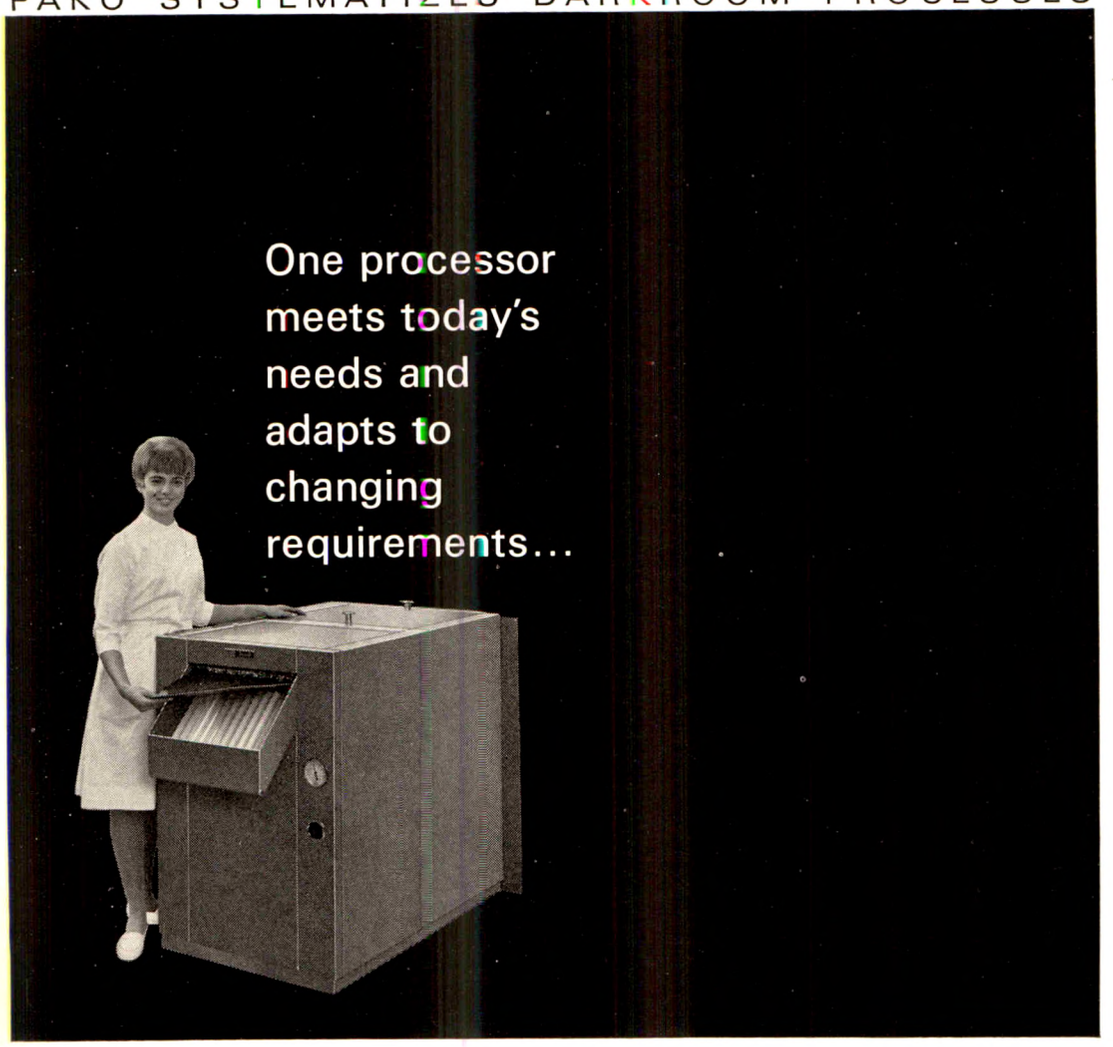
Shortcomings of radiography in the study of the liver have, in many cases, been overcome by the use of ultrasonic laminography. Cirrhosis of the liver appears readily identifiable with technics that are relatively easy to master and are painless and innocuous to the patient.

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"...[pulmonary embolism] may exist in a grave form for a considerable time without objective signs being present on physical examination or routine chest films."[1]

Pulmonary embolism is a mimic. Because its symptoms resemble those of other cardiorespiratory diseases—particularly myocardial infarction[2,3] and pneumonia[4]—investigators have long sought simple and certain methods of diagnosing it.

Many diagnostic clues—but often no clinical picture

Until a few years ago diagnosis depended primarily on the clinical history, physical findings, chest films, electrocardiograms, angiography, and pulmonary function studies. Each of these was helpful. Sometimes not even *all* of them were conclusive.

Surgery, prolonged immobilization, metastatic carcinoma and trauma often precede pulmonary embolism—but are not necessarily followed by it. Pain, dyspnea, hemoptysis may signal pulmonary embolism—but they aren't necessarily peculiar to it. The electrocardiogram may be normal in spite of it.[5] And there is no pathognomonic radiographic picture of pulmonary embolism.[5]

To be clinically valuable, however, a new diagnostic test should meet two criteria:
1. it should be correlated with known pathology; i.e., it should be carefully compared with other diagnostic procedures;
2. it should offer information not attainable as easily or as safely by accepted tests.[6]

Pulmonary arteriography meets the first criterion and is a most reliable diagnostic tool. It is, however, a time-consuming procedure and one that requires experienced personnel.[2]

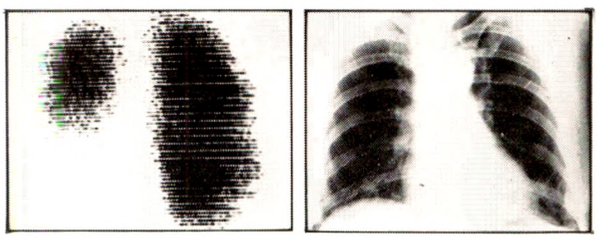
"...lung scintiscanning can detect an obstruction of the pulmonary circulation as soon as it is established."[7]

Not only is the diagnostic procedure of lung scanning both safe and easy,[2] but there is information that is not attainable on chest films. "...it appears that the lung scan can point to the site of the embolic lesions before signs of lung infarction are recognizable on plain chest films."[1]

The scan and the x-ray shown confirm this statement.* The photoscan of this female patient, aged 58, was taken August 13, 1965 with Albumotope-LS (Squibb Aggregated Radio-iodinated [I^{131}] Albumin [Human]). Pulmonary emboli are clearly evident. The x-ray, taken the same day, shows no radiographic evidence of pulmonary emboli.

Lung scanning meets both criteria for a clinically valuable diagnostic test. Findings are correlated with pulmonary function studies, angiography, pathology and the clinical state of the patient. And, scanning with Albumotope-LS has been proven to be "simple, rapid, and safe in the diagnosis, localization and

*Illustrations furnished through the courtesy of George V. Taplin, M.D., Harbor General Hospital, Torrance, California.



ultimate fate of pulmonary emboli."[2] But the lung scan should not be relied upon as the only diagnostic procedure in the diagnosis of pulmonary embolism.[1]

Dosage and Scanning Procedures: Recommended scan doses of 150 to 300 microcuries of Albumotope-LS (Squibb Aggregated Radio-iodinated [I^{131}] Albumin [Human]) depending on the instrumentation available and the technics employed. Scanning can immediately follow administration of slow intravenous injection or be delayed up to 1 to 1½ hours depending on preferred technic.

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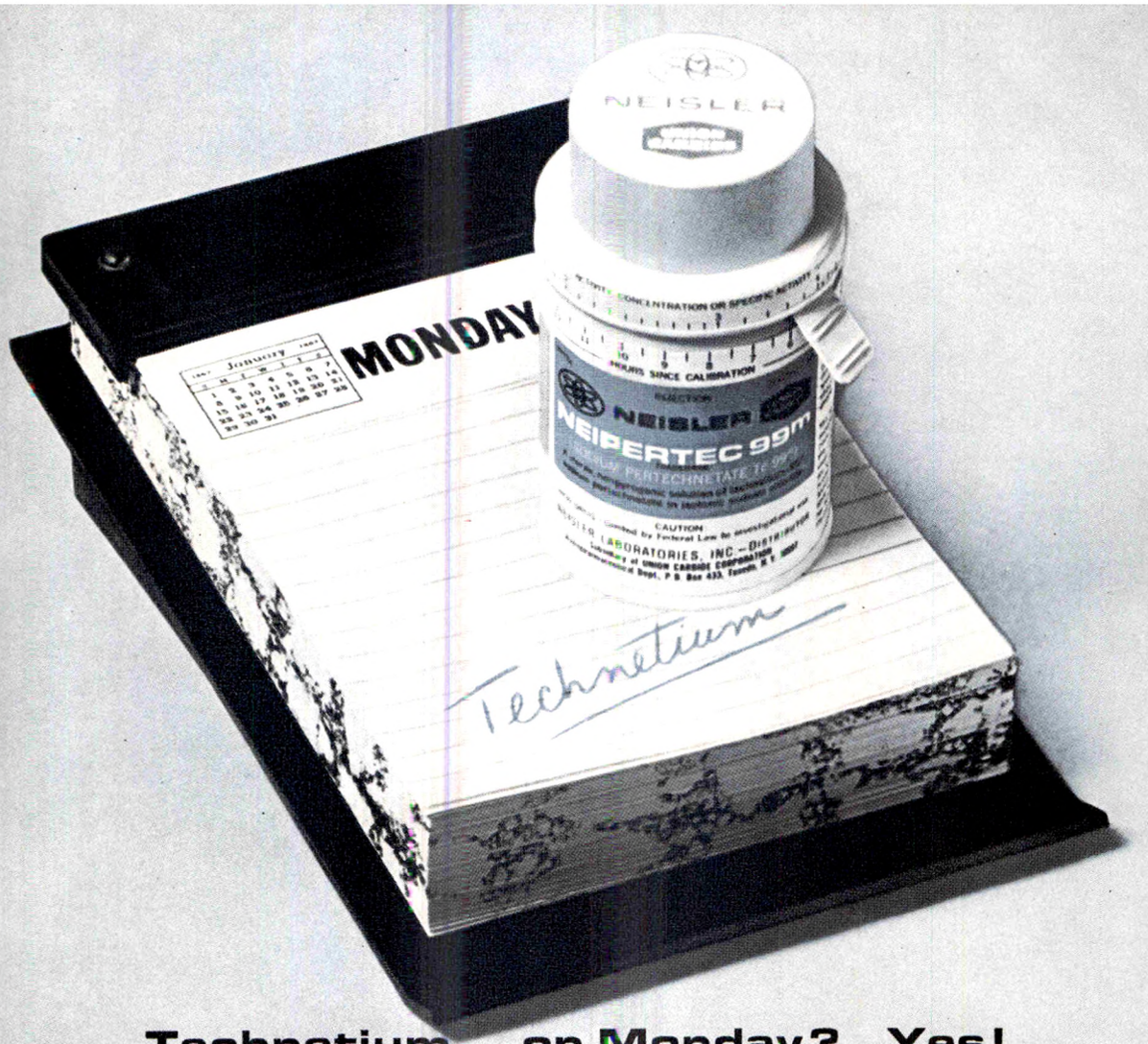
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1. J. G. McAfee, C. F. Fueger, H. S. Stern, H. N. Wagner, Jr. and T. Migita: Tc^{99m} pertechnetate for brain scanning, *J. Nucl. Med.*, 5:811, 1964.

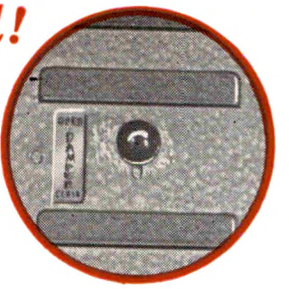
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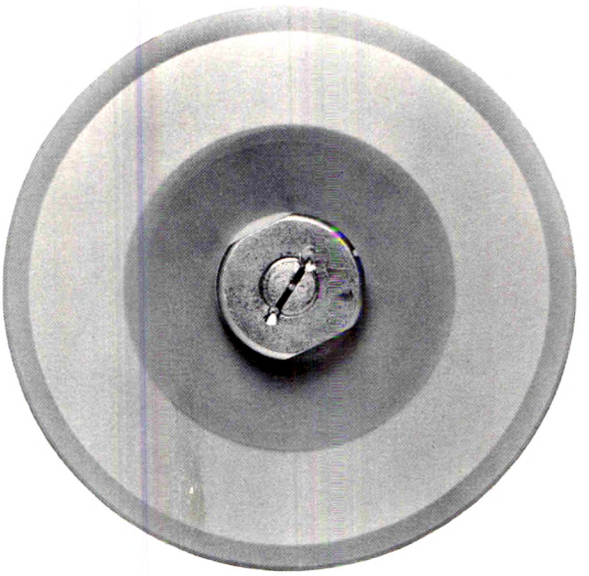
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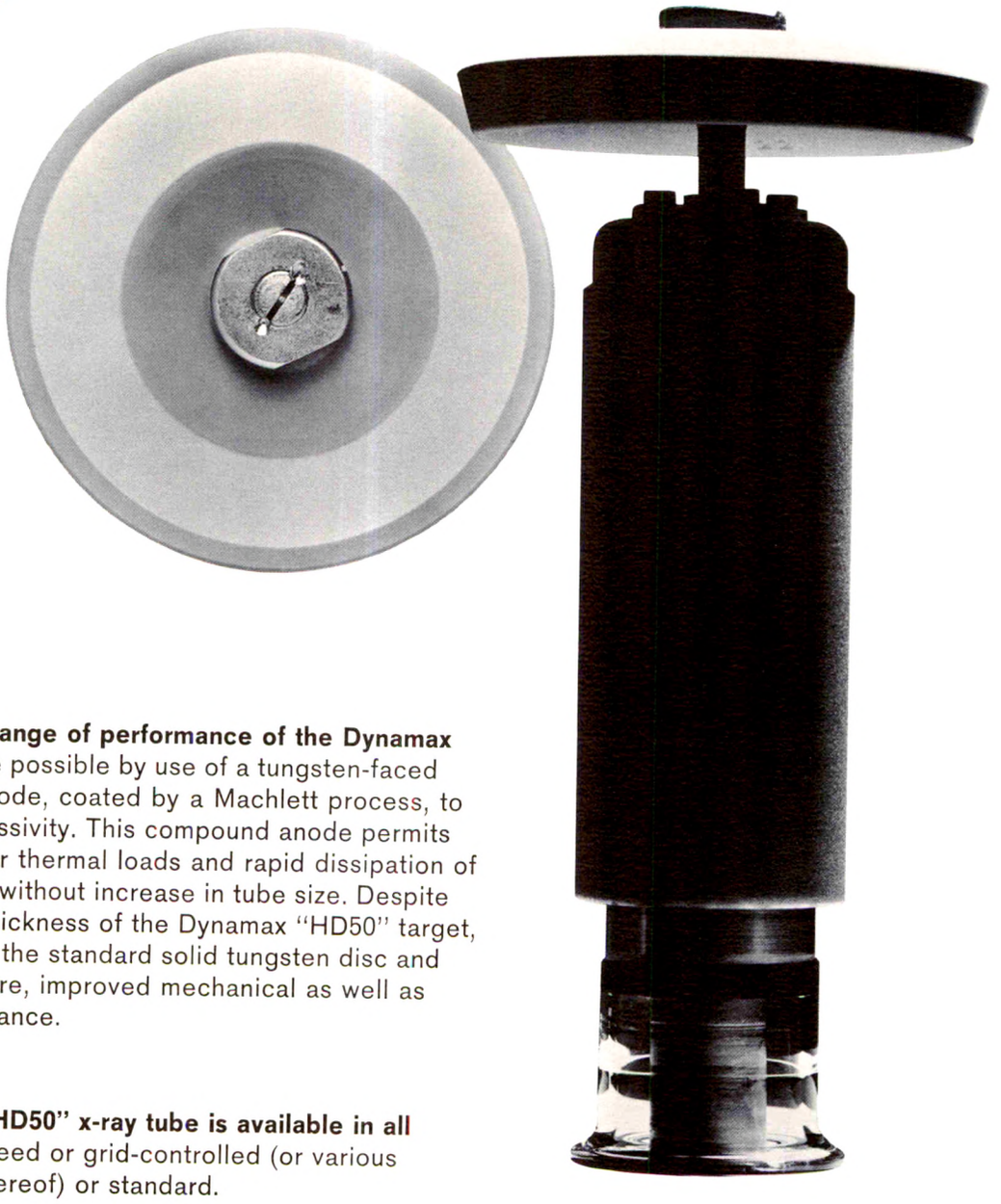
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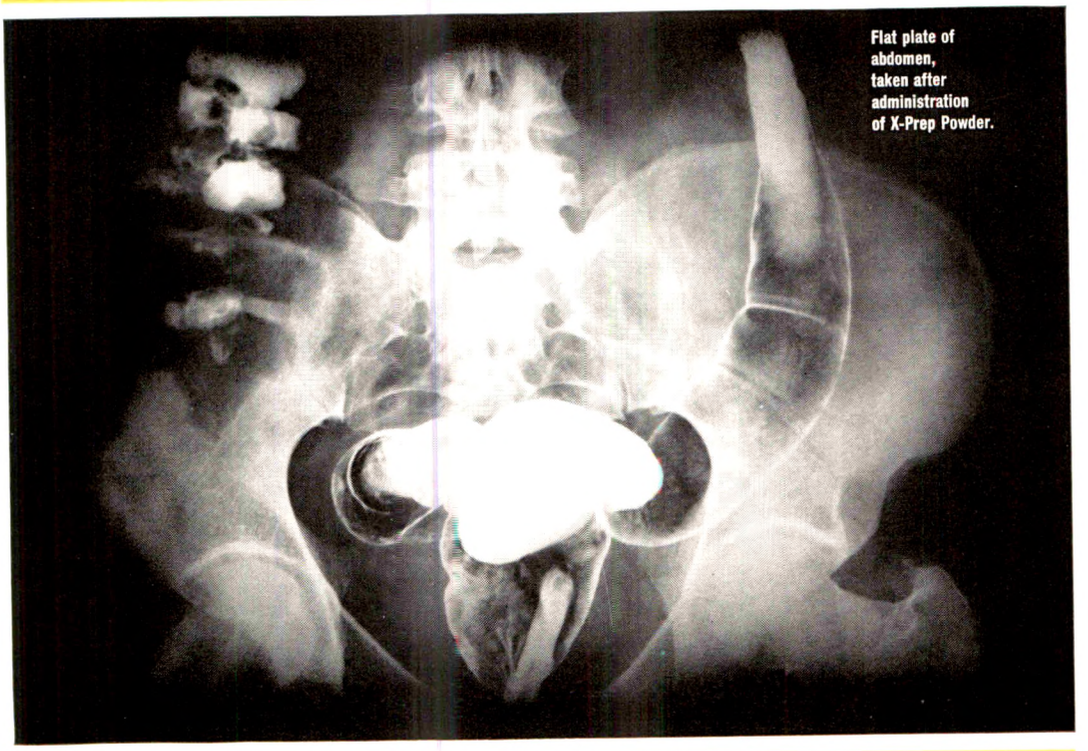


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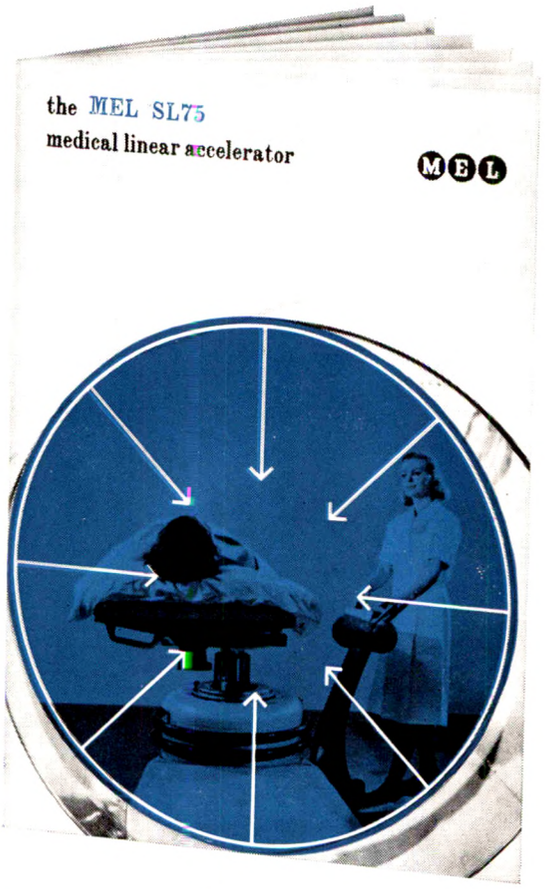
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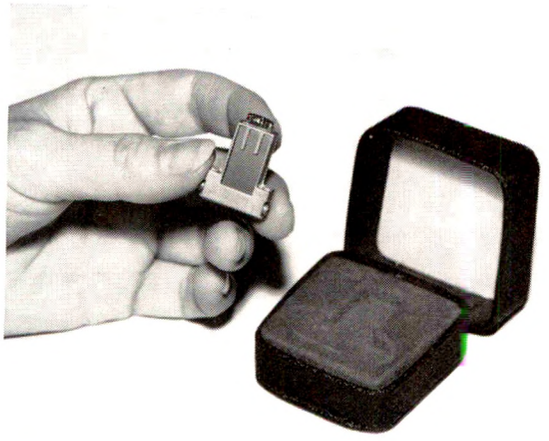
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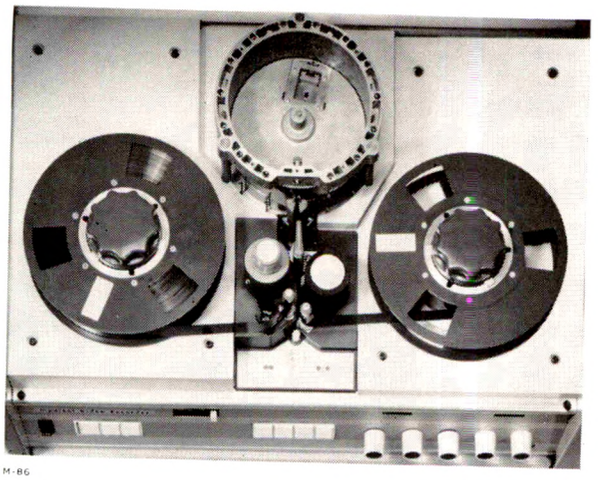
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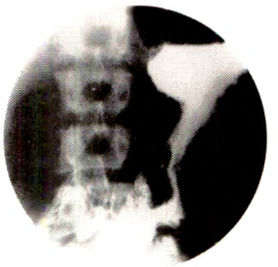
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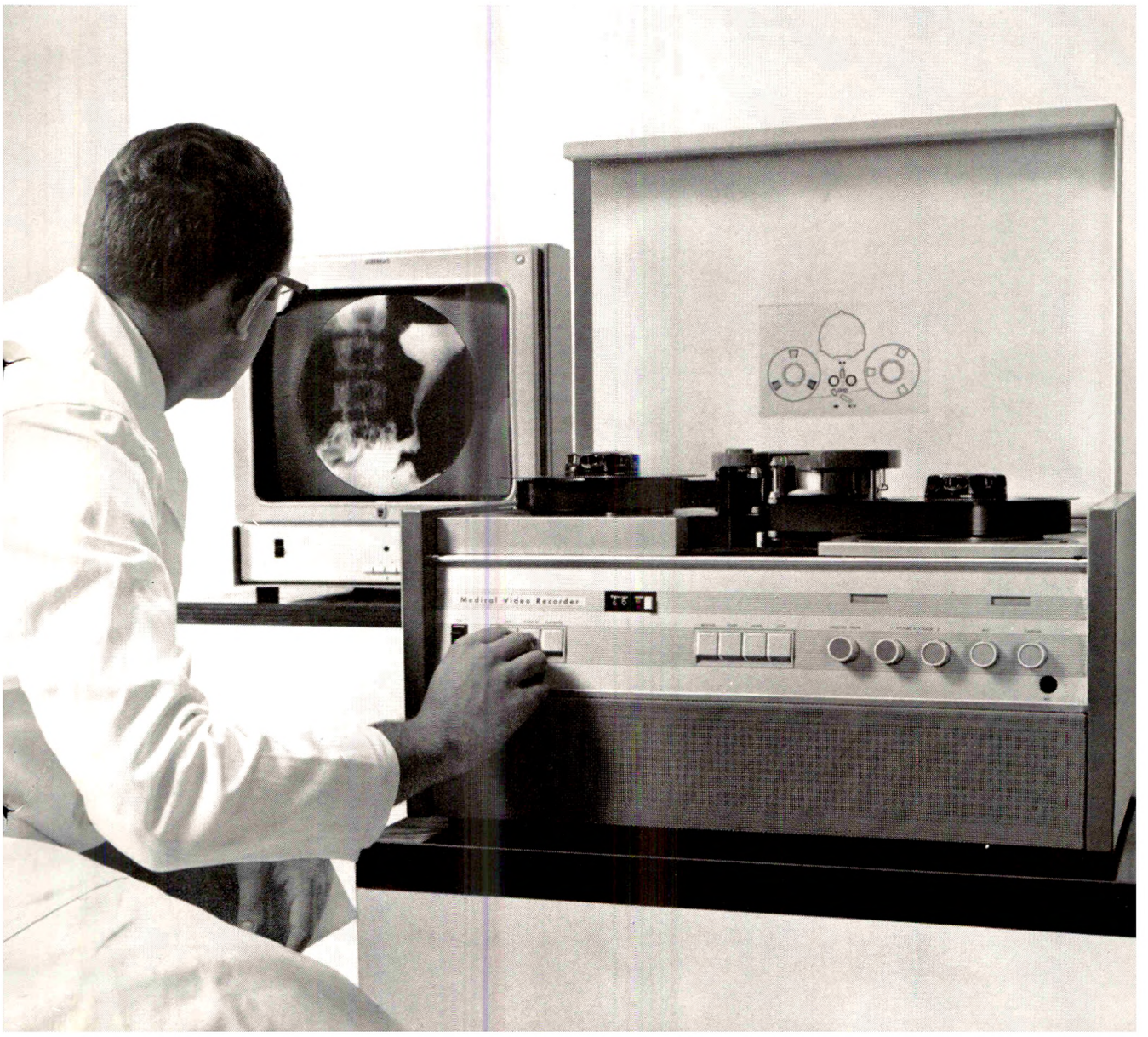
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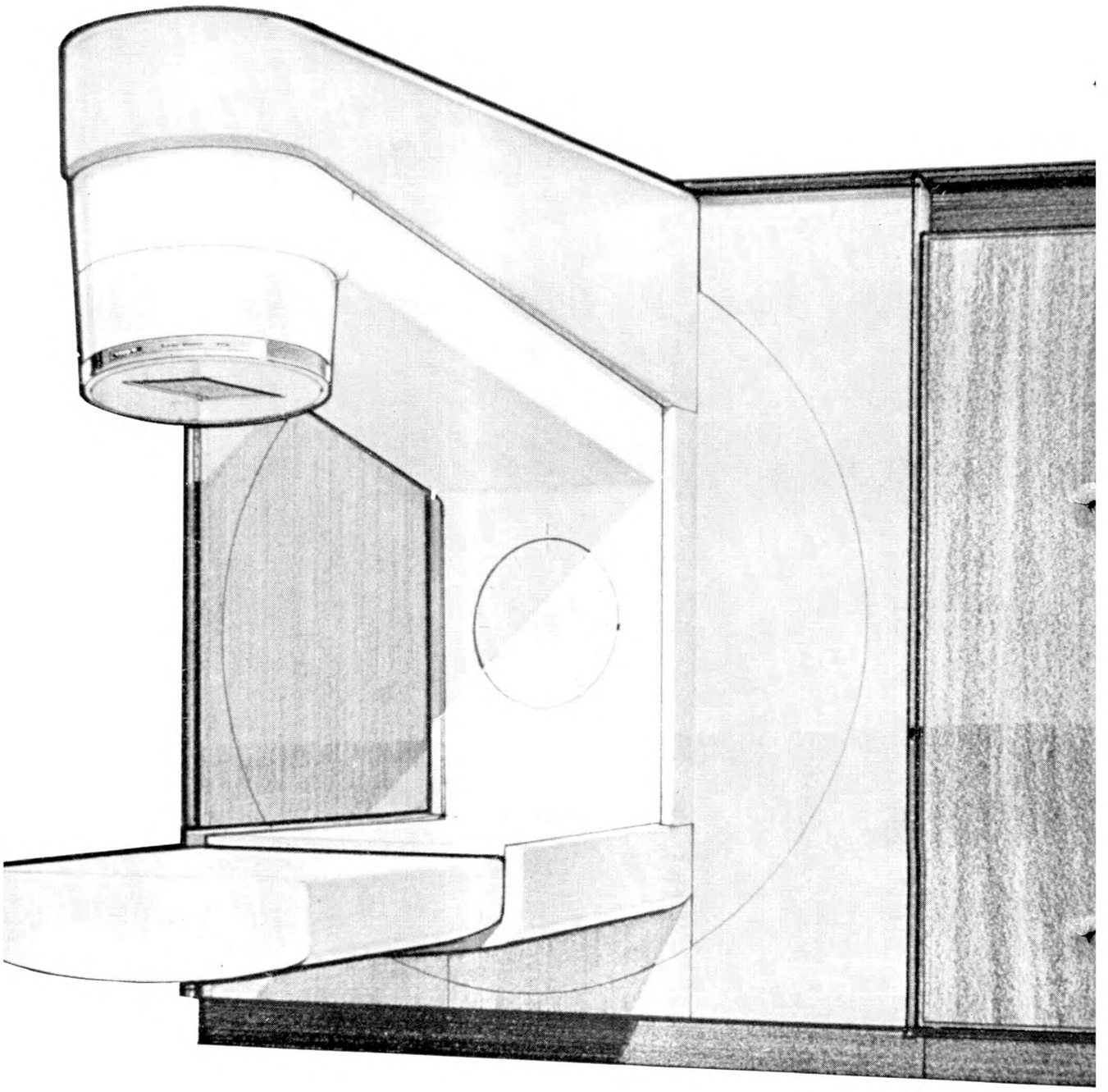
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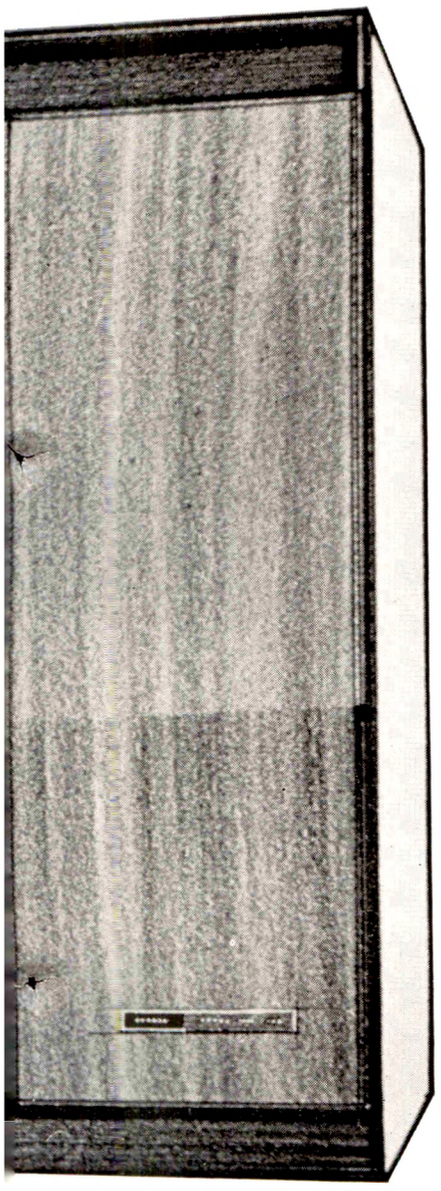


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Advanced Therapy High X-ray output and the retractable beam shield on the Mevatron 8 make it especially useful for techniques such as hyperbaric oxygen therapy and whole body irradiation. Its wide energy range and its capability for increased depth dose allows treatment of deep-seated tumors with fewer fields. Electron therapy is especially effective because of the minimal X-ray contamination of the beam (less than 0.1%).

Examples of associated therapy techniques include management of advanced cases of mycosis fungoids and Kaposi's Hemorrhagic sarcoma. You'll also find it easier to perform post-operative treatment of the rib cage and other areas where only skin penetration is involved, because the wide energy range of the Mevatron can be precisely controlled.

Research and Experimental Uses In addition to the many therapy uses of the Mevatron, you also get a unique research capability, to help you spread your initial investment over a broader range of productive functions. Examples include demonstration and investigation of radiation effects on medical, physical, and biological systems and the performance of in-vivo and in-vitro radiation studies.

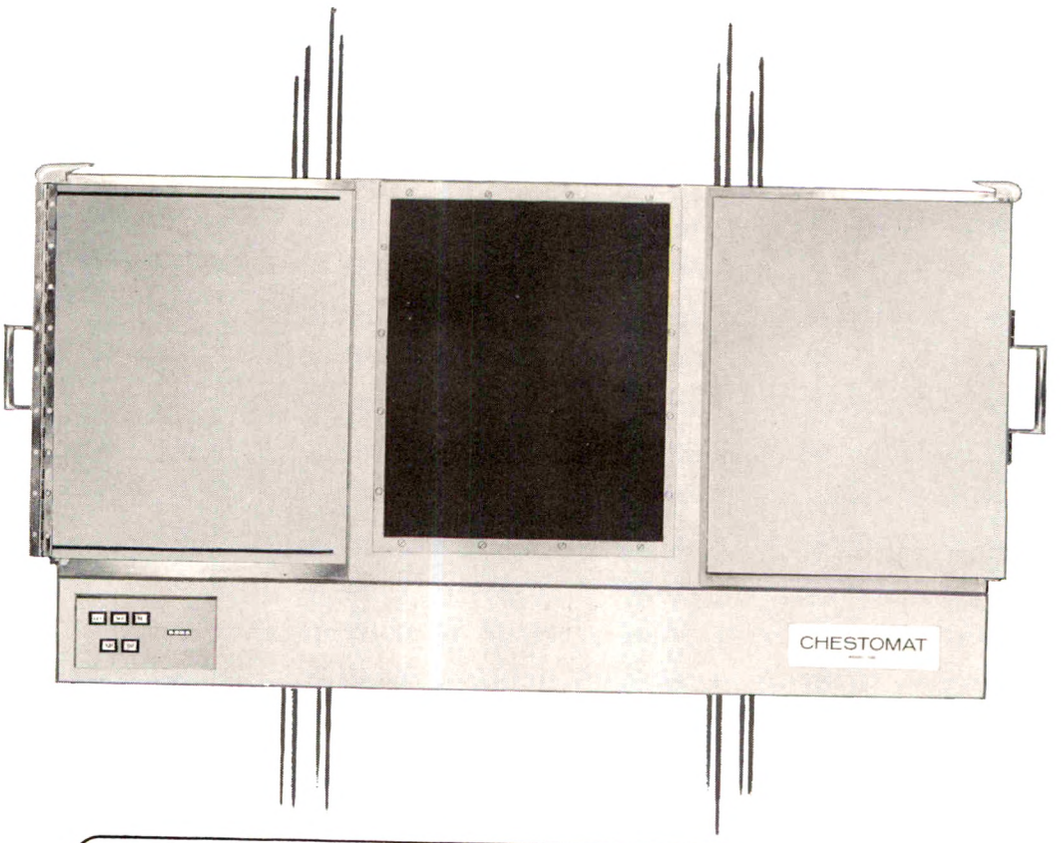
You can also use the Mevatron to produce neutrons, thus providing short-lived radioisotopes for analysis, diagnosis and therapy. Additional uses of the Mevatron include bone and tissue sterilization and the bulk-sterilization of sutures and other hospital supplies.

Complete Planning Assistance The Mevatron 8 is the most versatile medical linear accelerator available today, and to make sure that you get the maximum effective use from your investment, Applied Radiation has a strong program of assistance. Numerous experts within the company, and qualified consultants, can help you plan every step of the linear accelerator installation, from initial financing considerations through installation and complete therapy and research program planning.

For a more detailed discussion of the therapy/research capabilities of the Mevatron 8, write or call Applied Radiation in Walnut Creek, California.

APPLIED RADIATION

WALNUT CREEK, CALIFORNIA 94596 / TEL.: (415) 935-2250



CHESTOMAT

MODEL 100

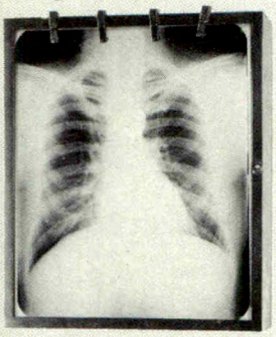
The CHESTOMAT permits routine and specialized 14x17 inch radiographs of excellent quality without the need of individually loaded cassettes. Automatic operation allows rapid handling of patients in routine work—and the same apparatus is ideally suited for stereo work.

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Rx for good radiographs



The right film.

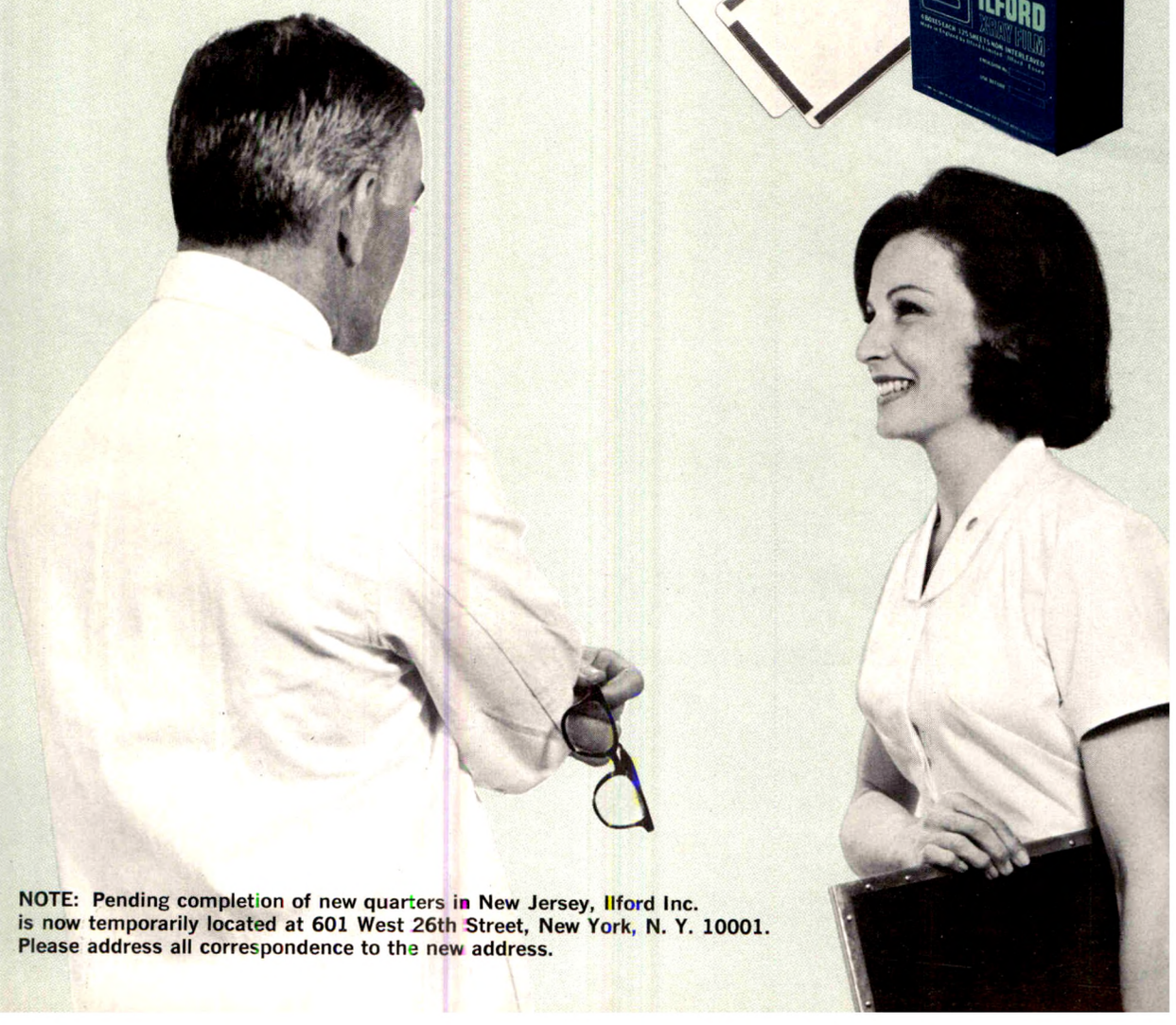
The right screen.

The right film for most radiographic investigations is one which offers high contrast, medium speed, fine grain and very low fog level. Ilford Standard is that film—at a cost appreciably lower than for other films of comparable quality. *Standard is compatible with the new "half-cycle" or "double-capacity" automatic processing techniques.*

The right screen must be fast, with outstanding definition—and Ilford Fast Tungstate Intensifying Screens are the ultimate in the field; their definition is equal to that of most screens with half the speed. Put these two fine products in the hands of a skilled technician and you will have gone a long way toward improving your radiographs.

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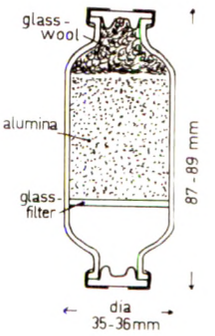




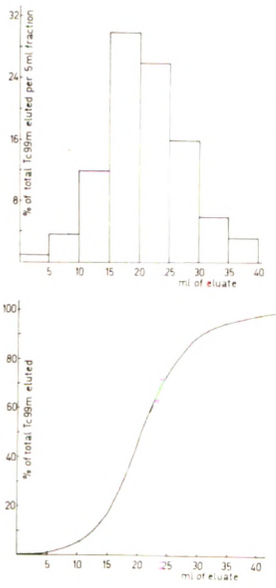
NOTE: Pending completion of new quarters in New Jersey, Ilford Inc. is now temporarily located at 601 West 26th Street, New York, N. Y. 10001. Please address all correspondence to the new address.

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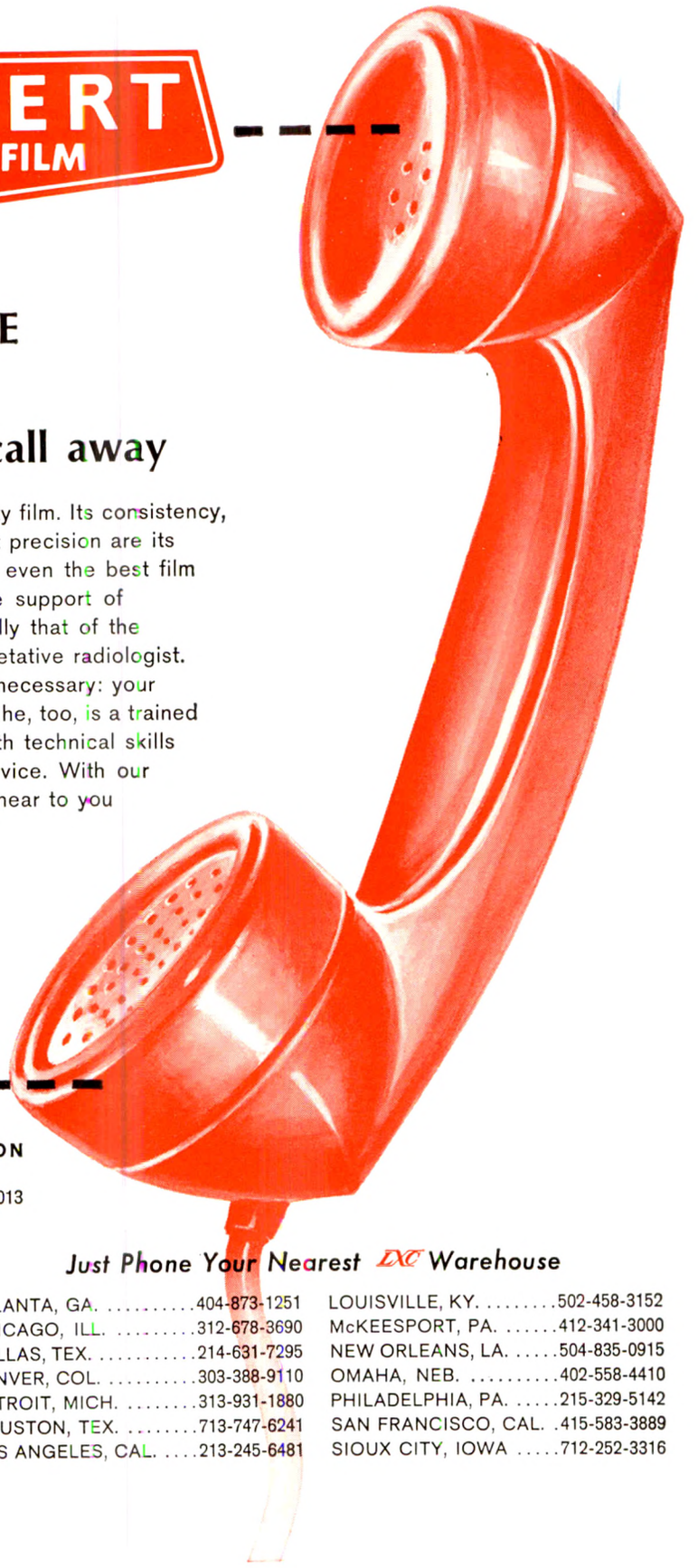
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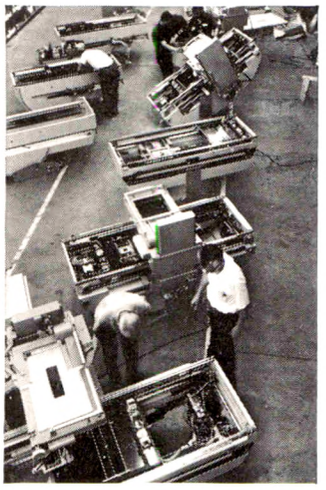
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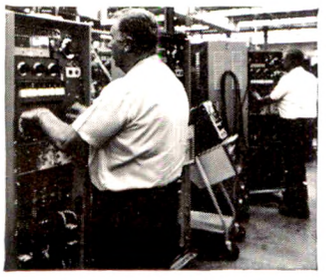
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The new Dynapix® was designed for the busy Radioisotope Department.

(Too demanding of information to sacrifice imaging quality for the sake of speed. And vice versa.)



To date the Radioisotope Department with a large patient load and the need for maximum information per picture has really had only two kinds of choices: either (1) good images, slowly achieved, or more recently (2) higher speeds at the expense of picture quality. But since neither choice is quite appropriate to the need, there now comes a third option, the Dynapix. Design goals: *maximum information / minimum time.* Is this actually possible? Isn't compromise inevitable?

A totally new approach obviated the need for compromise. The Dynapix is a completely unique radioisotope imaging device which has, among other things, ten (10!) scintillation detectors working in concert, each detector with its own focusing collimators, each detector with its own electronics.
The practical import of this?

High speed
Since each of the ten scintillation detectors has its own electronics, the whole assembly can count many times faster than a single detector of *any* size. There is no faster detection system now

available; clinical scans take from a fraction of a minute to a few minutes. Ideal for recording dynamic processes or for multiple views. Minimizes discomfort to patient by reducing time of immobilization.

High imaging quality

Dynapix pictures yield maximum information to the clinician. Since each crystal has its own focusing collimators (choice of three), spatial resolution equivalent to that of conventional scanners can be obtained without the "out of focus" problem of large single crystals. The Dynapix features contrast enhancement which produces 64 grey shades proportional to the counting rate above background.

Large scanning field

The scanning field is a full 10" x 20" which effectively permits imaging of most organs in a single scan or high-speed whole body scanning with several adjacent scans. This field size is at least 2½ times larger than that of other high-speed instruments and has no distortion at the edges.

Other important features, briefly

(1) Three types of data readout provide maximum flexibility: TV screen, Polaroid camera (positive or negative film), and scaler.

(2) Magnetic tape storage of *total* data for rapid playback at variable data enhancement settings.

(3) Easy to use: experienced workers in this field can be getting usable Dynapix scans on the day of installation.

(4) The Dynapix produces pictures which are familiar and can be easily related to one's prior experience.

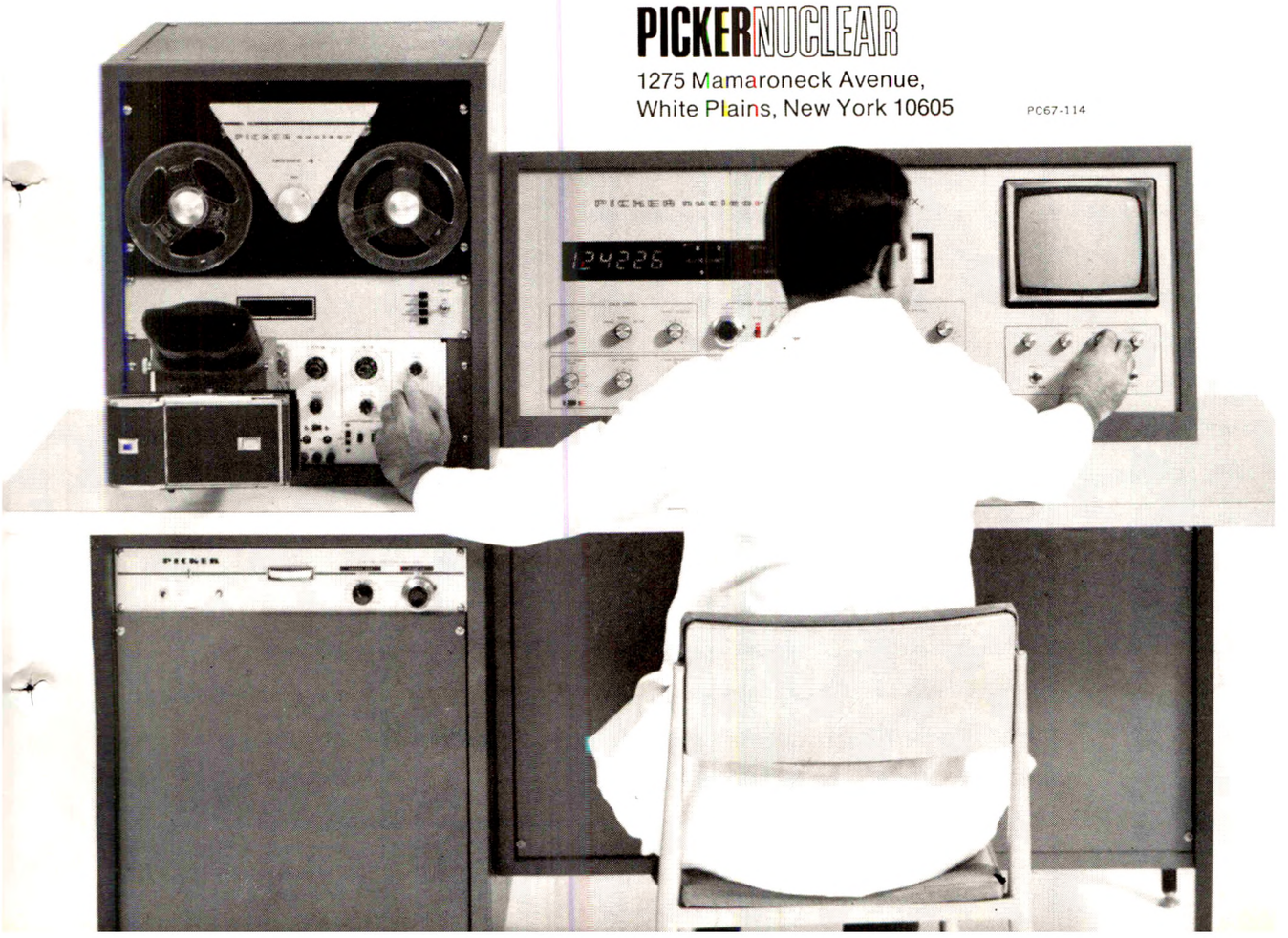
Finally

The Dynapix has been proven in major clinical installations. This enables us to provide proof of the many claims above. Accordingly, the object of this entire presentation is to solicit such challenges, and to leave you with the simple message: Dynapix provides *maximum information/ minimum time:* Now demand proof by requesting data file 114X

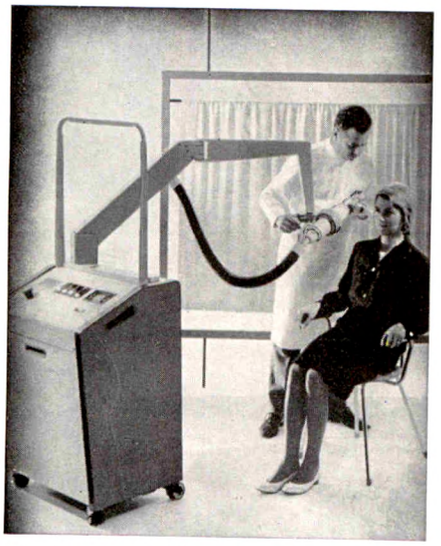
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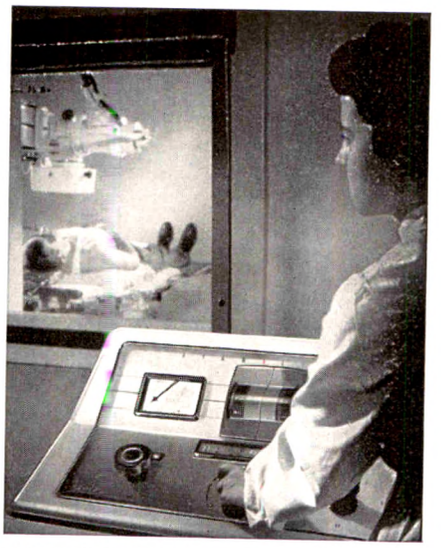
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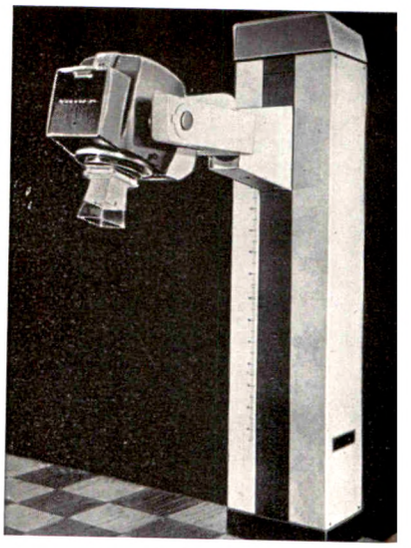
From single room to great center



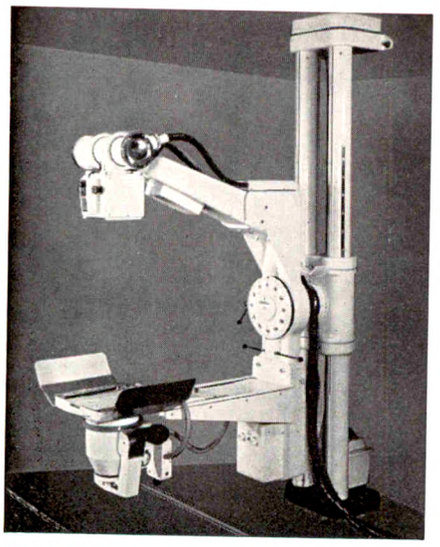
10—50 kV DERMOPAN 2



300 kV STABILIPAN



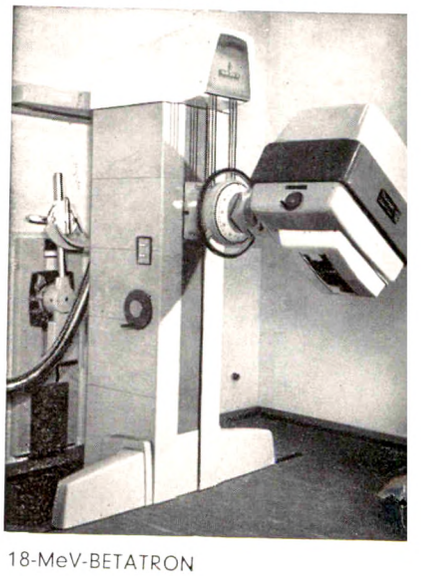
Cs 137 CAESA-GAMMATRON



SIMULATOR

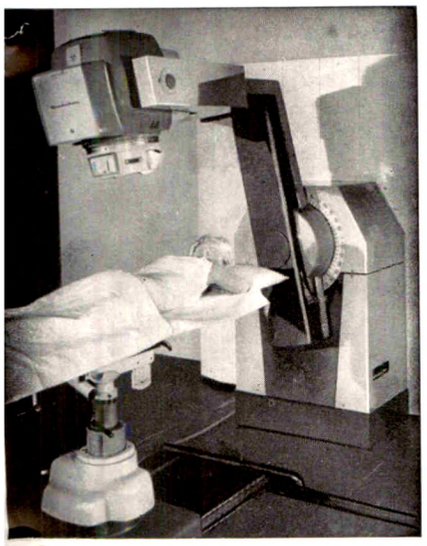
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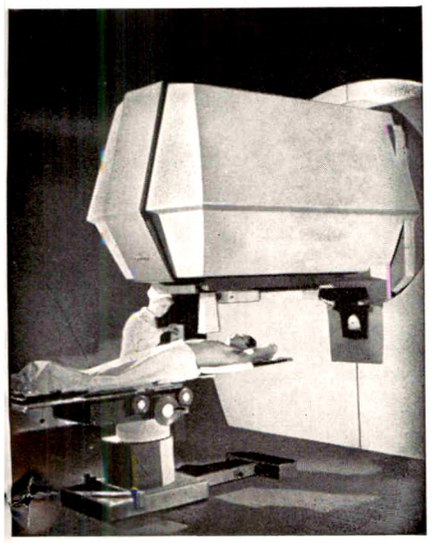


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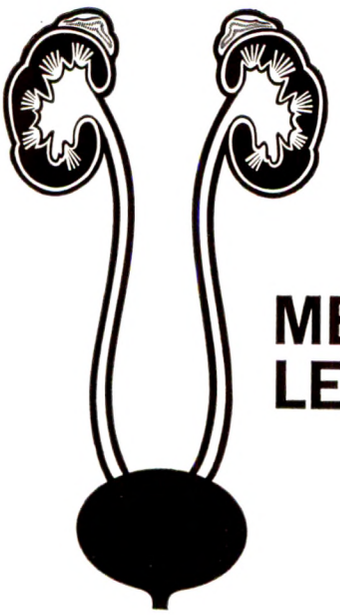
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Side effects: Severe, life-threatening reactions are rare; when they occur, they suggest hypersensitivity to the contrast agent. Transient flushing and nausea during injection may occur. In rare instances, anaphylactoid reactions may occur.

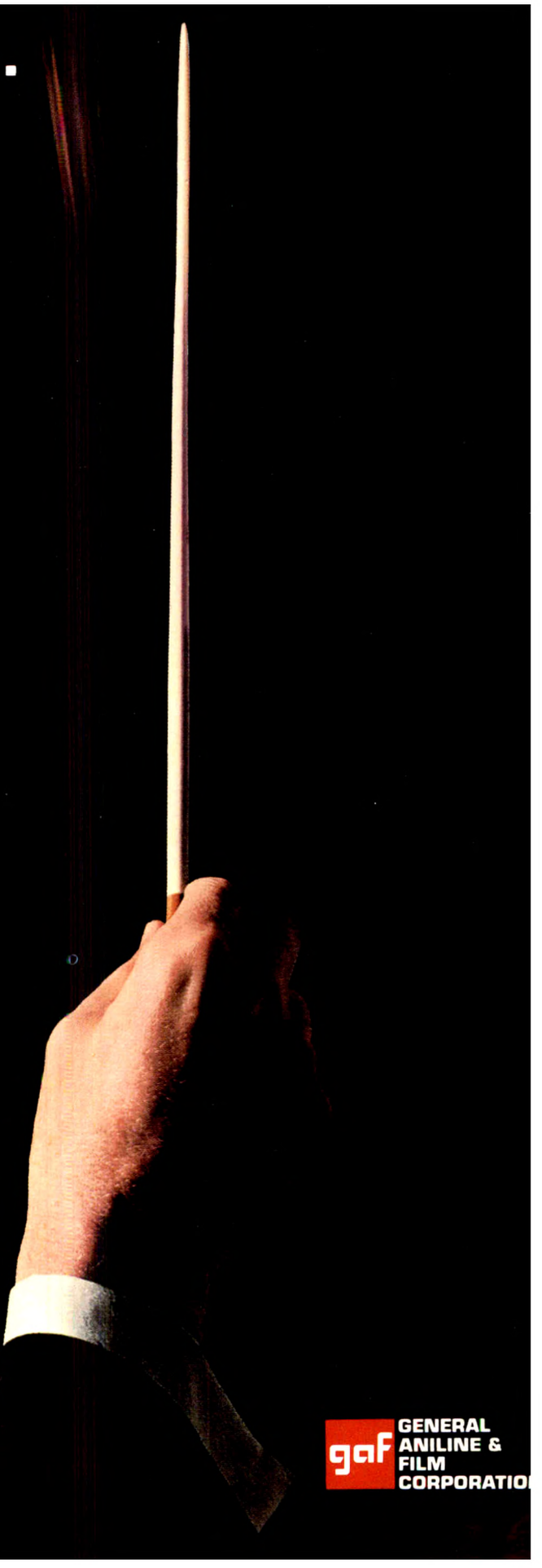
Precautions: I.V. test dose may be given. Use with caution in the event of an untoward reaction to the test dose and in extreme age, severely debilitated patients, cyanotic infants, patients with chronic pulmonary emphysema, advanced arteriosclerosis, severe hypertension, cardiac decompensation, and recent cerebral embolism or thrombosis. The possibility of thrombosis should be borne in mind when percutaneous techniques are employed. For full information, see Product Brief.

*Margulis, A. R., and Heinbecker, P.: Am. J. Roentgenol. *86*:103 (July) 1961.

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FROM
Daniel Bernoulli, M.D.
(1700–1782)



TO
G. B. Venturi
(1746–1822)



TO
Tar Gard
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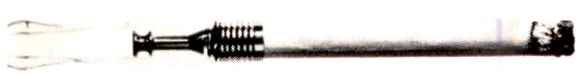
In 1738, Daniel Bernoulli, M.D. (received his Doctorate of Medicine with a thesis on the action of the lungs), member of a Dutch family distinguished in mathematics and other sciences, solved the equation now known as Bernoulli's Law and advanced the kinetic theory of gases and fluids.

In 1791, G. B. Venturi, an Italian physicist, applying Bernoulli's Law investigated the principle by which the kinetic energy or 'fluid flow' of gases and liquids could be measured.

Application of this principle led to the development in 1886, of the Venturi Tube (Clemens Herschell, American engineer), the physical basis of the tar trapping efficiency of Tar Gard.

Tar Gard — how it works. In Tar Gard, as cigarette smoke is drawn through the Venturi Unit into the mouthpiece, the pressure-energy of the smoke is accelerated (to approx. 200 mph) and then stopped abruptly by an impingement barrier, where tars are trapped. The tars you see in the above unretouched photograph were isolated by Tar Gard from the smoke of only four *filter* cigarettes.

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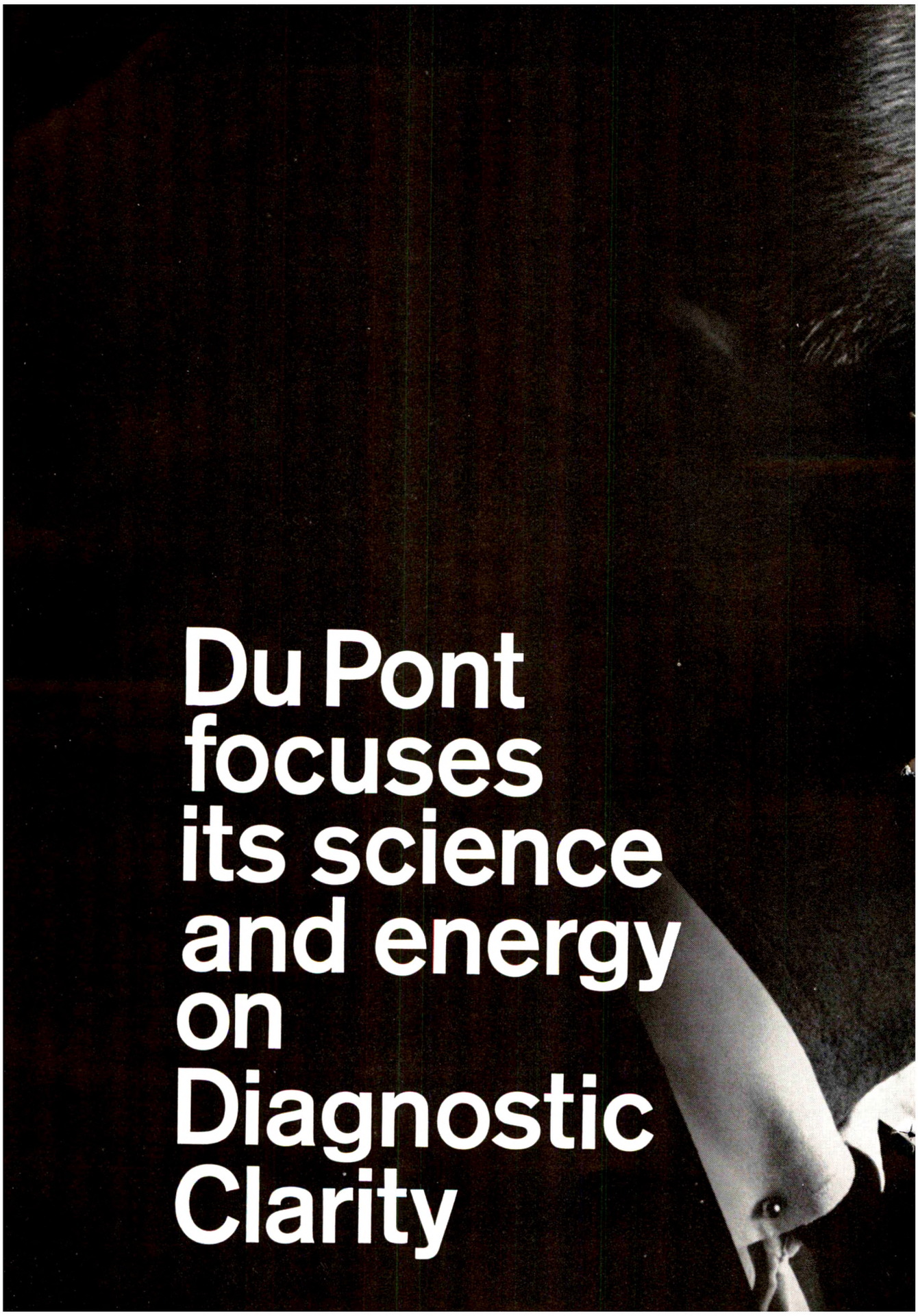
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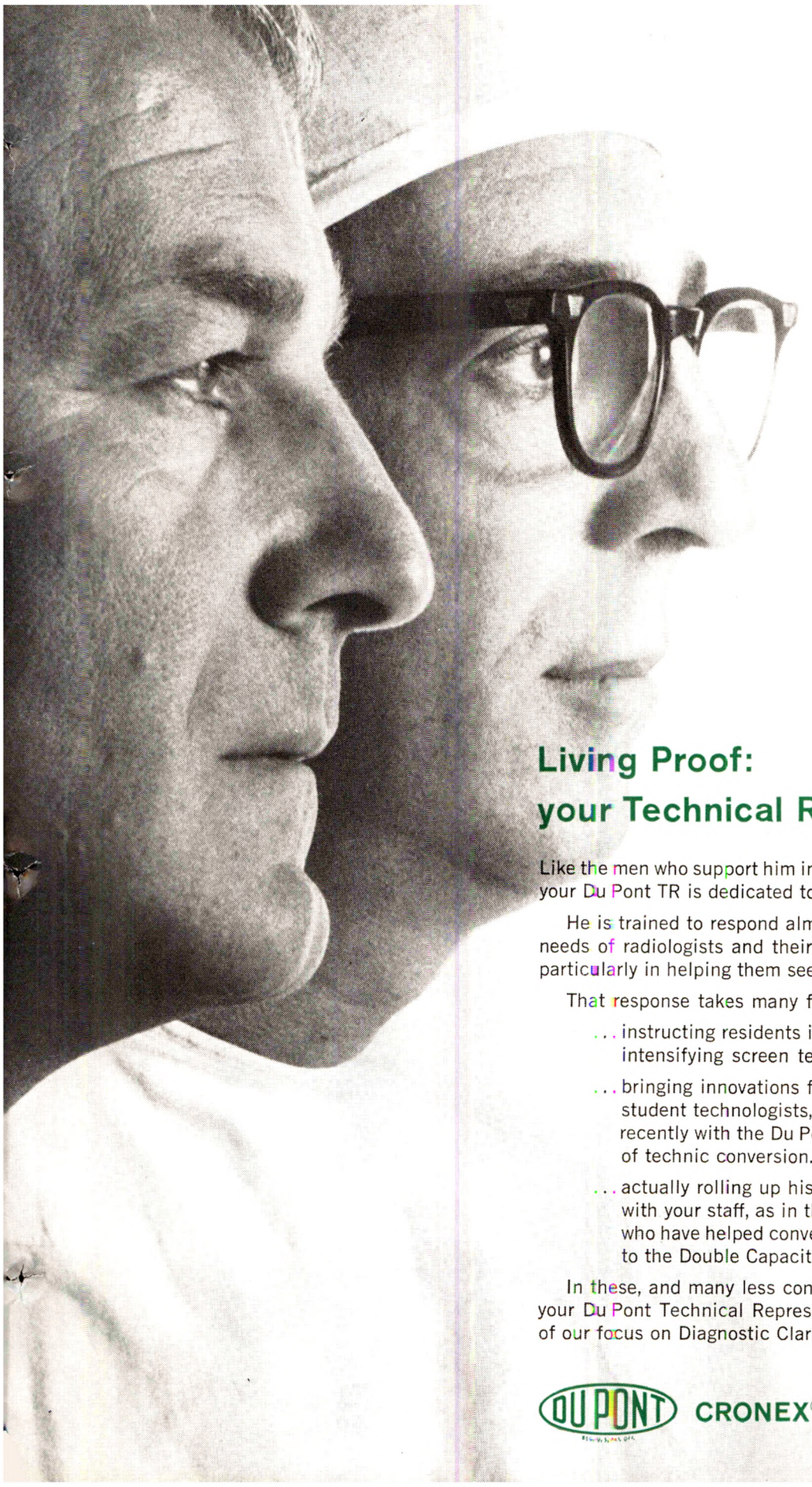
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- . . . actually rolling up his sleeves and working with your staff, as in the case of the TRs who have helped convert automatic processors to the Double Capacity system.

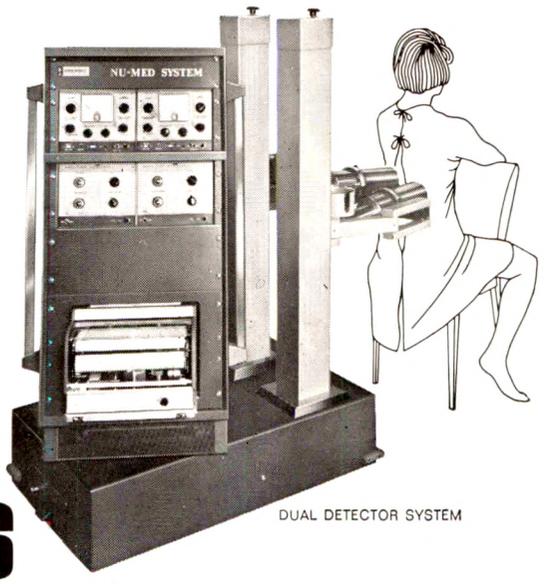
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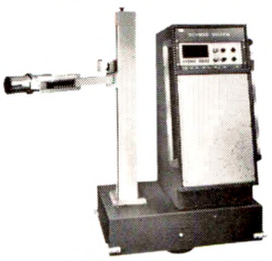
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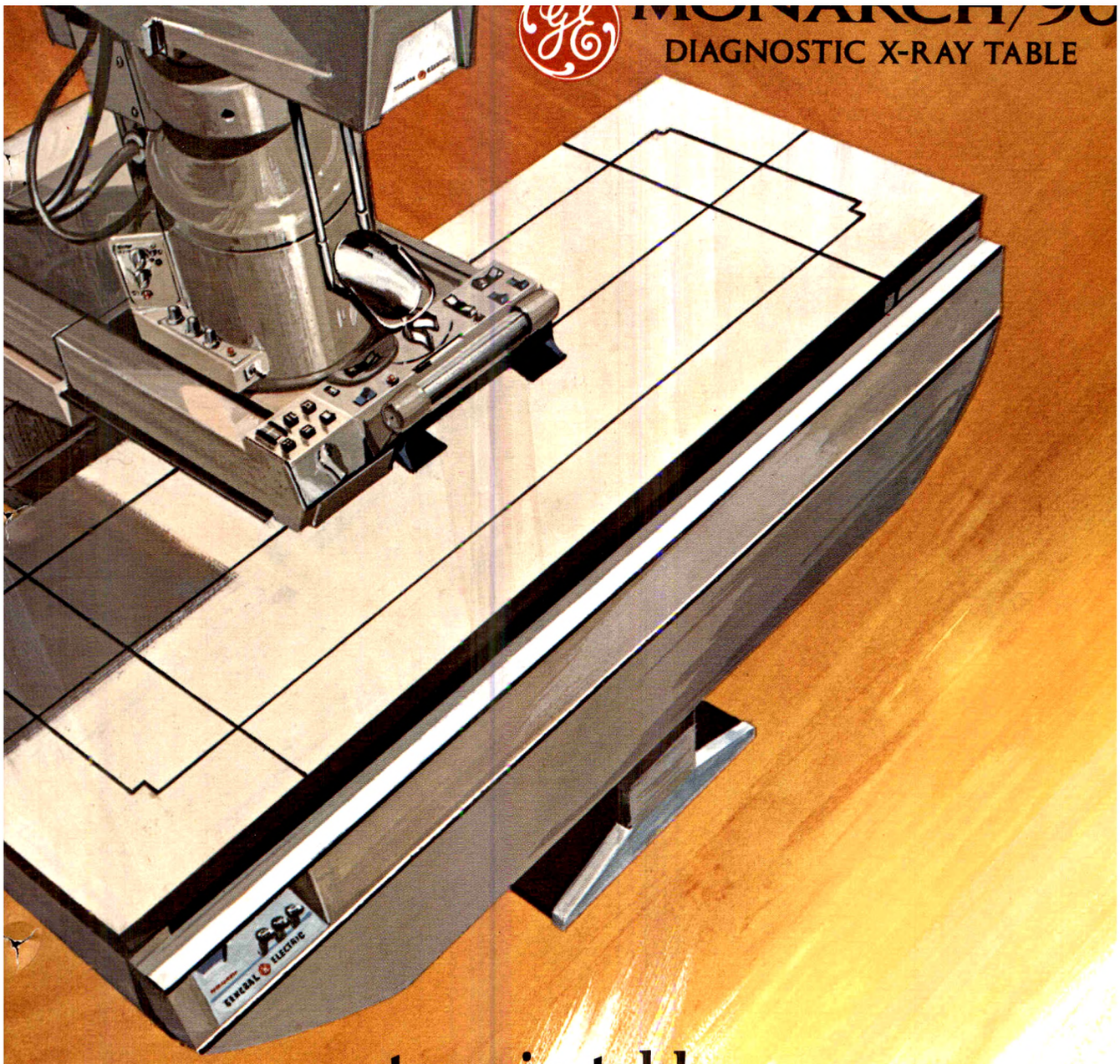
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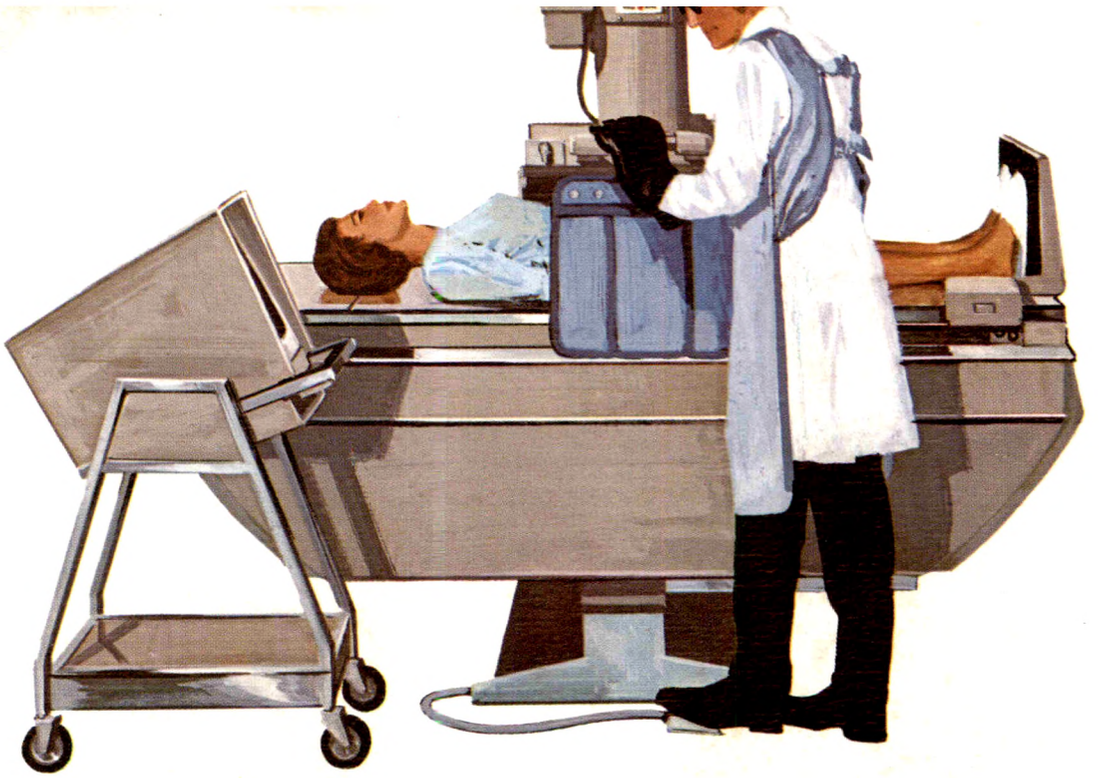


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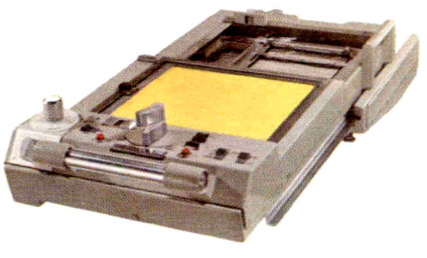
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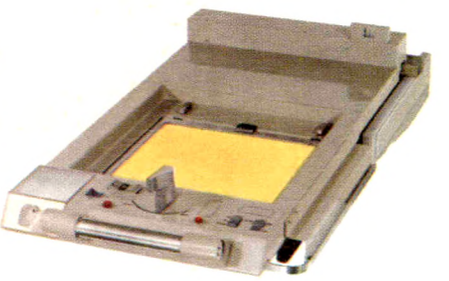
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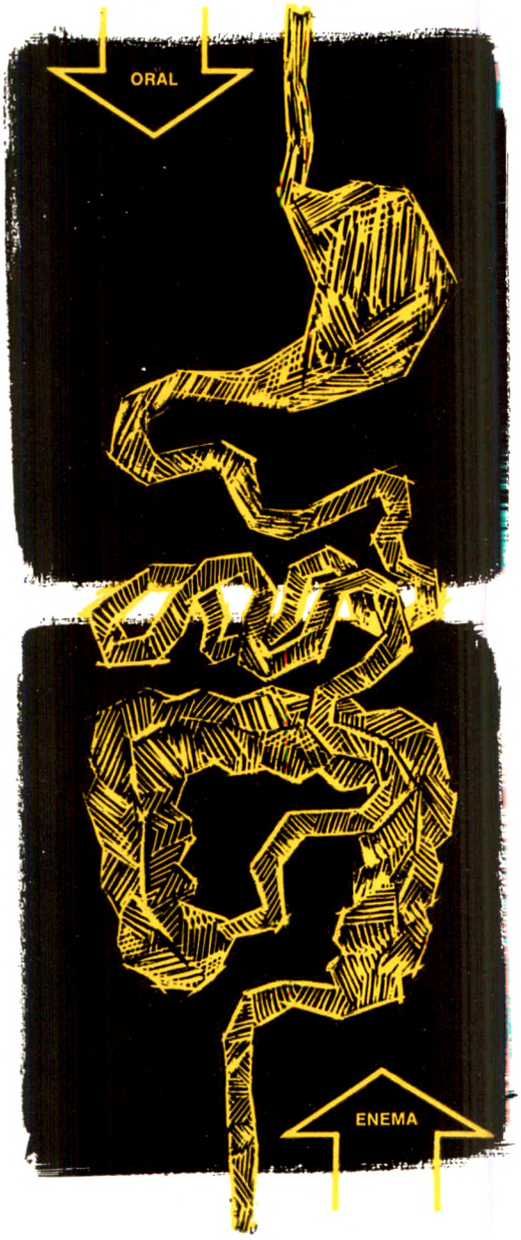
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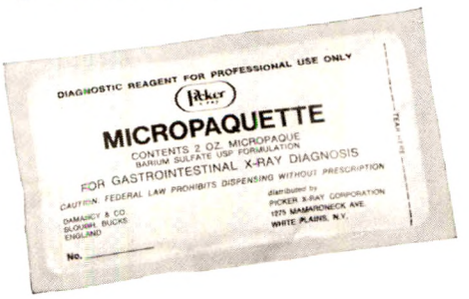
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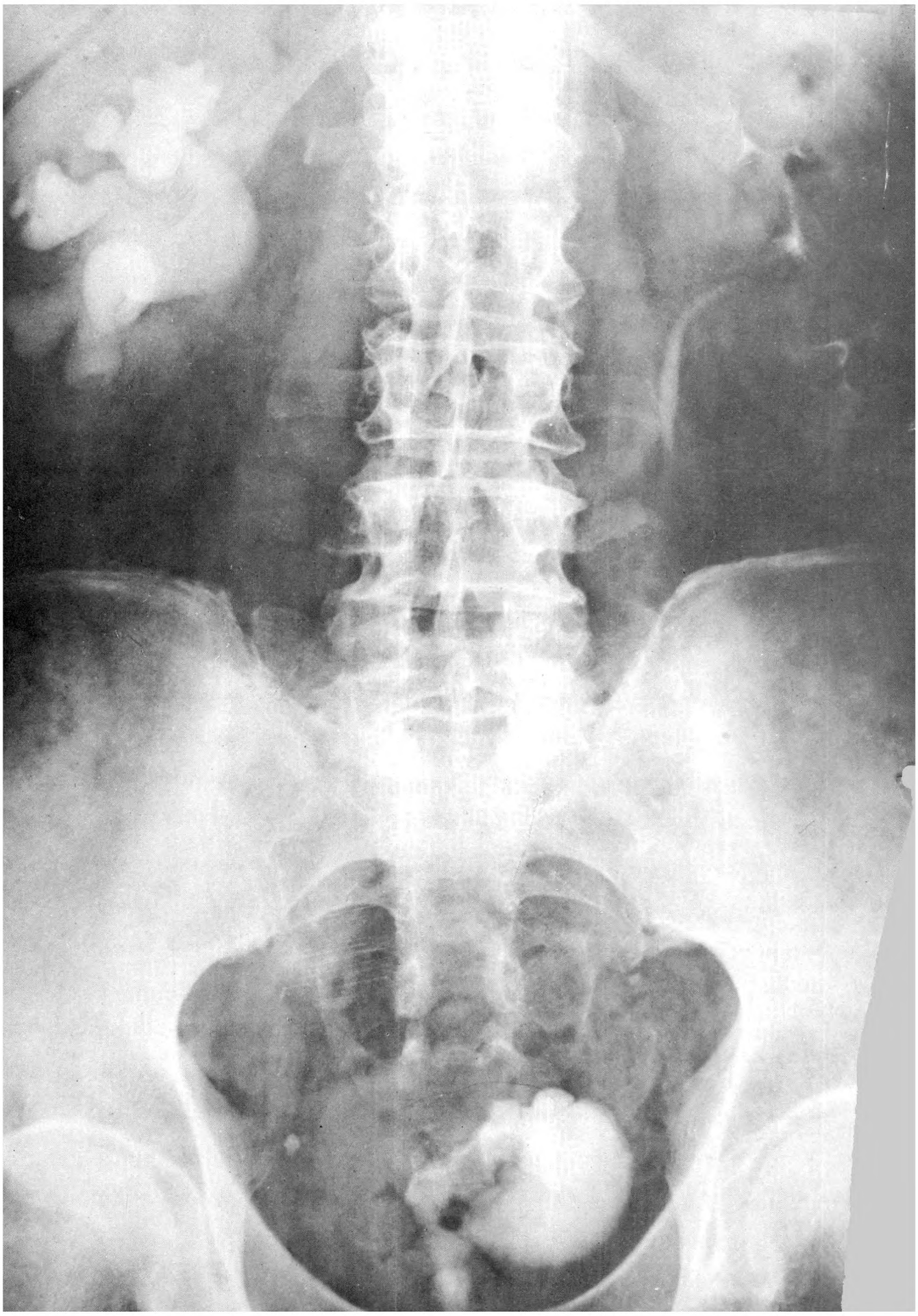
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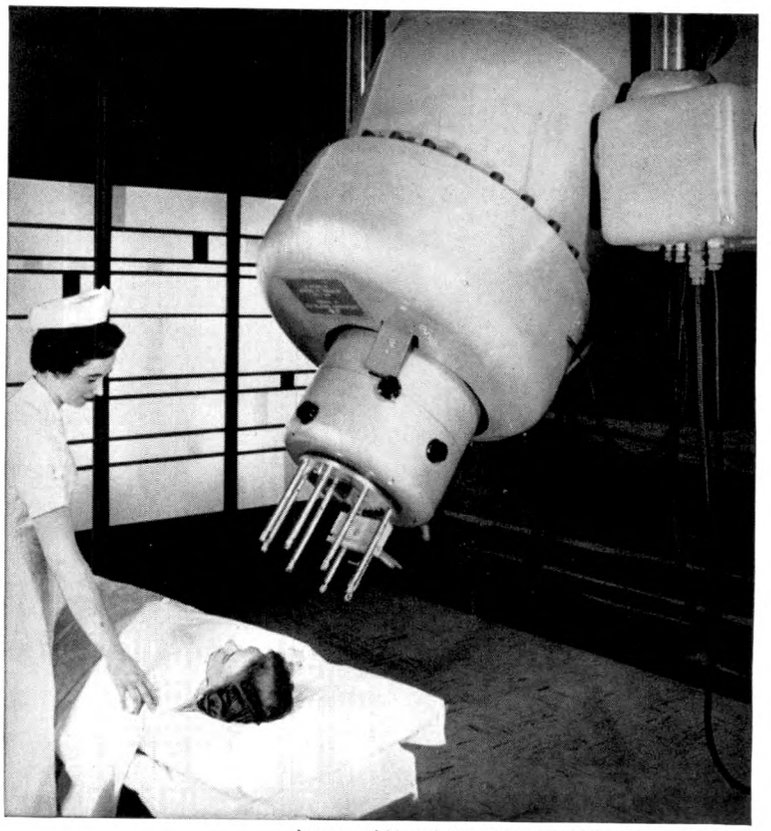
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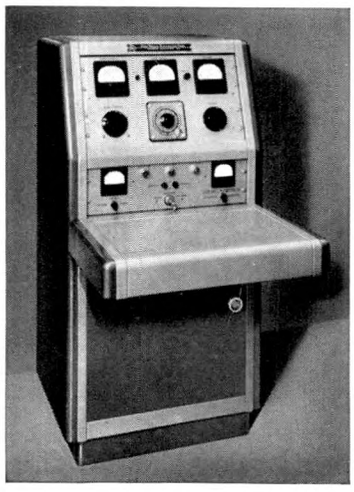


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LATERAL LUNG SCANNING, ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS*

By EDGAR L. SURPRENANT, M.D.†
LOS ANGELES, CALIFORNIA

PHOTOSCANNING the lungs after the intravenous injection of macroaggregated radioalbumin (I^{131}) is a safe and useful diagnostic procedure.[6,7] Currently, the major use of this technique is in the detection of ischemic areas secondary to pulmonary embolism, although many other pathologic conditions produce pulmonary ischemia. Anterior and posterior views of the chest have been commonly employed. These views demonstrate both lungs simultaneously and allow comparison between the two lungs. Additional information can be derived by obtaining other views of the chest. The purpose of the author is to describe the pulmonary anatomy seen on the lateral views and to discuss several advantages of this projection.

MATERIALS AND METHODS

A commercial scanner was utilized according to directions of the manufacturer.* All scans were made with the 19 hole collimator and 10 per cent suppression; scanning speed was 90 cm./min. Subjects were injected intravenously with 300 μc of macroaggregated radioalbumin (I^{131}) and the chest was scanned immediately. A variety of body positions was employed during the injection which will be described in the discussion of individual scans. The detector scanned only in the horizontal plane. Maximum count rates varied between 15,000 and 25,000 counts/min. in the anterior or posterior projection, and approximately 25 to 50 per cent less in the lateral projections. The anterior view was usually obtained first, followed by the right lateral view (subject lying on his left side) and the left lateral view (subject on his right side). The same calibration was used for both lateral views. Occasionally, posterior views were obtained. In each position, a roentgenographic film was placed under the patient and an exposure was made immediately after the scan.

Figure 1 shows the method of scanning in the left lateral projection. Three metal markers were placed on the upper lateral chest wall and their locations were marked

* Pho-Dot Scanner, Nuclear Chicago.

* Presented at the Fourteenth Annual Meeting of the Association of University Radiologists, Little Rock, Arkansas, May 13–14, 1966.
From the Department of Radiology, The UCLA Center for the Health Sciences, Los Angeles, California.
† Winner of Memorial Medal Award of the Association of University Radiologists, 1966.

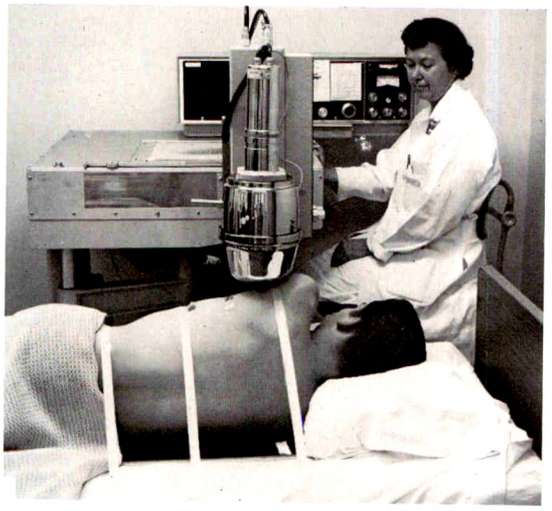


FIG. 1. Demonstration of technique for lateral lung scanning in bed. Note: (1) the film cassette is placed under the patient before scanning; (2) three markers (coins) are used. The central roentgen-ray beam will be directed through the central marker; and (3) the patient is taped firmly to the bed. The tape must adhere directly to his skin to prevent motion.

on the photoscan. The central roentgen-ray beam was perpendicular to the roentgenographic film and directed through the middle marker. Thus the degree of distortion due to magnification could be estimated when the photoscan and roentgenogram were compared. Magnification could be essentially eliminated by employing a 10 foot target film distance. The patient can be held relatively motionless by strapping with adhesive tape which adheres directly to his skin.

Isodose patterns were determined by means of a phantom constructed from a box

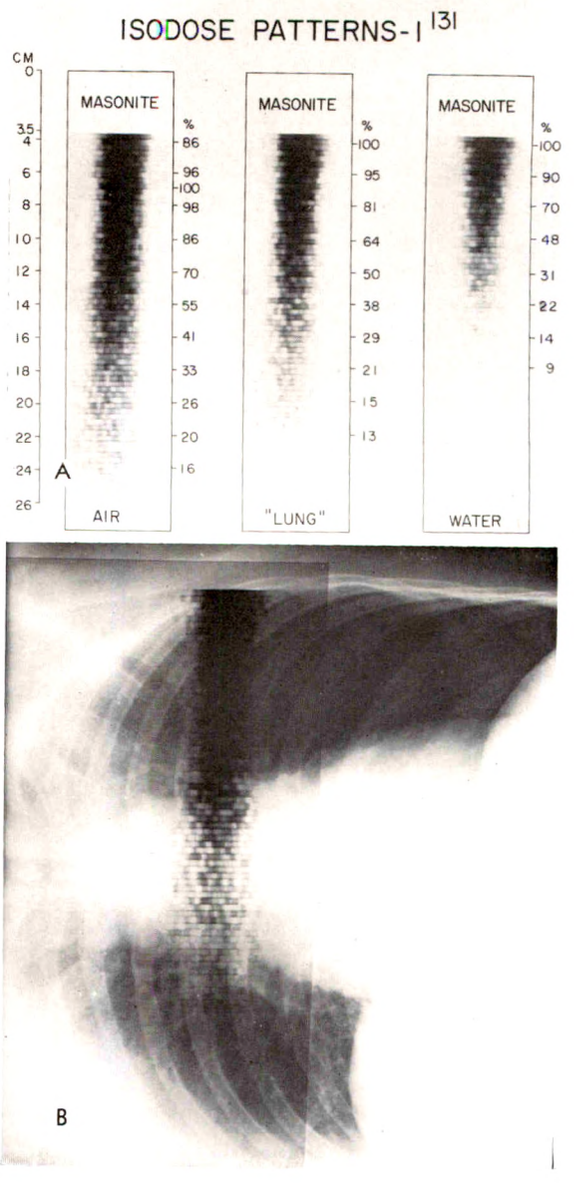


FIG. 2. (*A*) Isodose patterns were obtained with the 19 hole collimator. A 1 cm. diameter I^{131} source was suspended in 3 different mediums: air, oatmeal and water. Three and one half cm. of masonite was interposed between the scanner and the suspending medium. The masonite simulated chest wall and oatmeal was used as a substitute for aerated lung, both being organic material of similar density. With this geometry (19 hole collimator, absorption, back-scatter), the detector was most sensitive to radioactivity in the "lung" closest to it, 100 per cent at 4 cm. ("subpleural") compared to 50 per cent of the activity at 12 cm. and only 21 per cent at 18 cm. Eighteen cm. is approximately the distance from the surface of the lateral chest wall to the center of the mediastinum. Similar patterns for air and water are included for comparison. (*B*) The isodose pattern for "lung" is superimposed on a lateral decubitus chest roentgenogram. This illustrates that the proximal (upper) lung contributes most of the radioactivity recorded by the scanning detector.

with masonite walls 3.5 cm. thick. The patterns were derived from a 1 cm. diameter I^{131} source with the box filled with water, dry oatmeal and air (Fig. 2*A*). Oatmeal, an organic material with an average

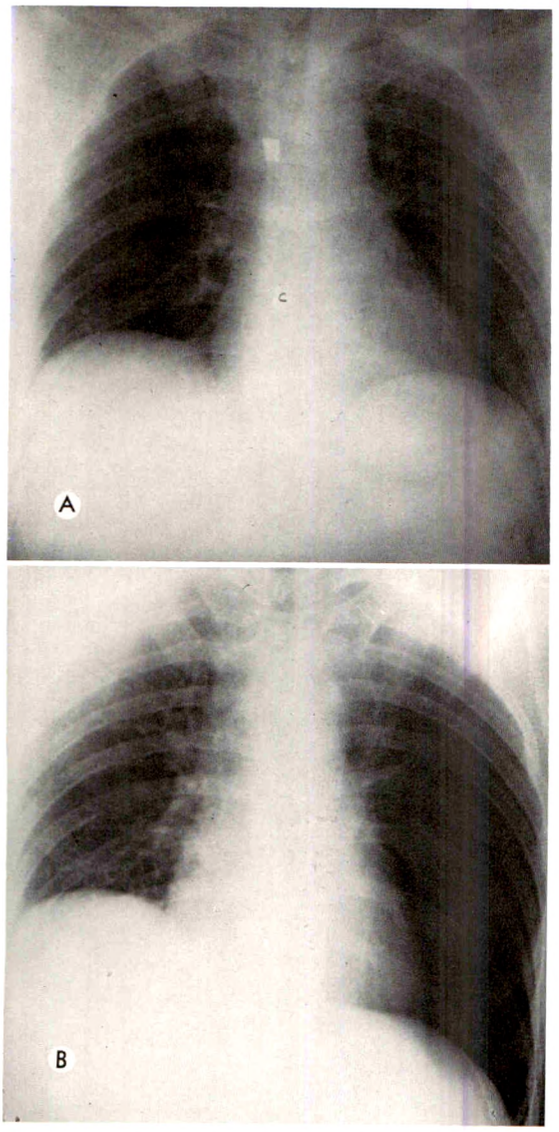


Fig. 3. (*A*) Supine chest roentgenogram obtained during quiet respiration. Both hemidiaphragms are at the level of the 8th posterior intercostal space. (*B*) Decubitus chest roentgenogram (right side down) of the same subject during quiet respiration. The left hemidiaphragm is down to the 10th posterior intercostal space while the right hemidiaphragm is still at the 8th. Also, the mediastinum has shifted to the right.

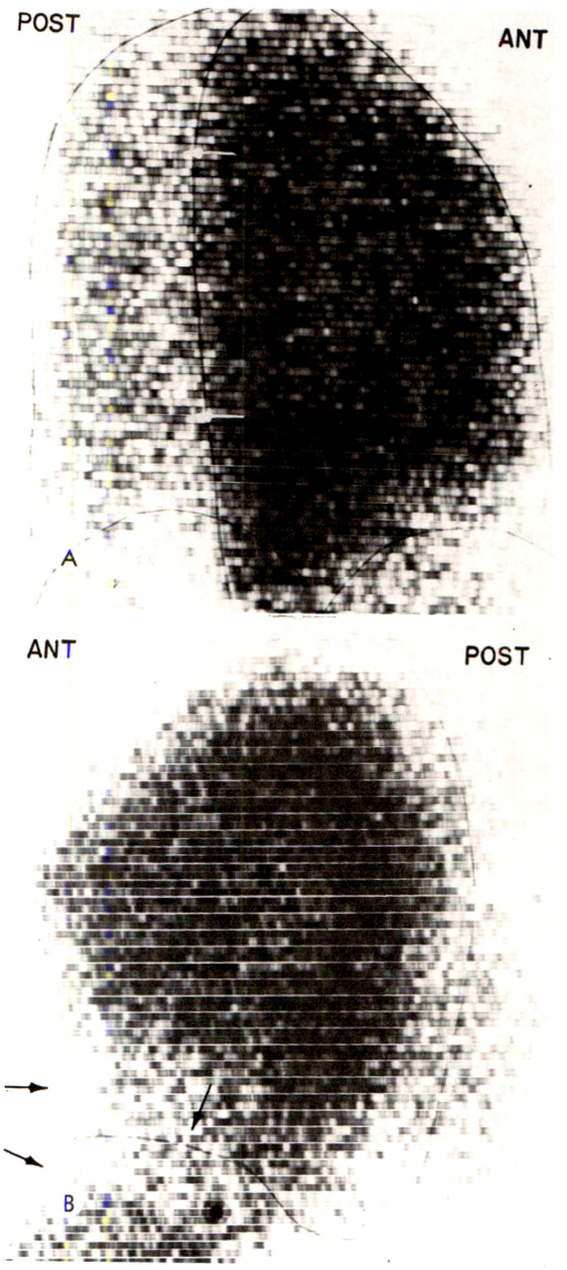


Fig. 4. (*A*) Right view of a normal subject who was not in a true lateral position. Note that much activity from the posterior aspect of the dependent lung was detected by the scanner since the superior hemithorax was rotated out of the way. (*B*) Left view of a subject with pectus excavatum (left horizontal arrows). Activity below the diaphragm is from the liver and spleen (right vertical arrow). Note that this subject was also rotated forward, allowing some activity from the distant lung to be seen posteriorly.

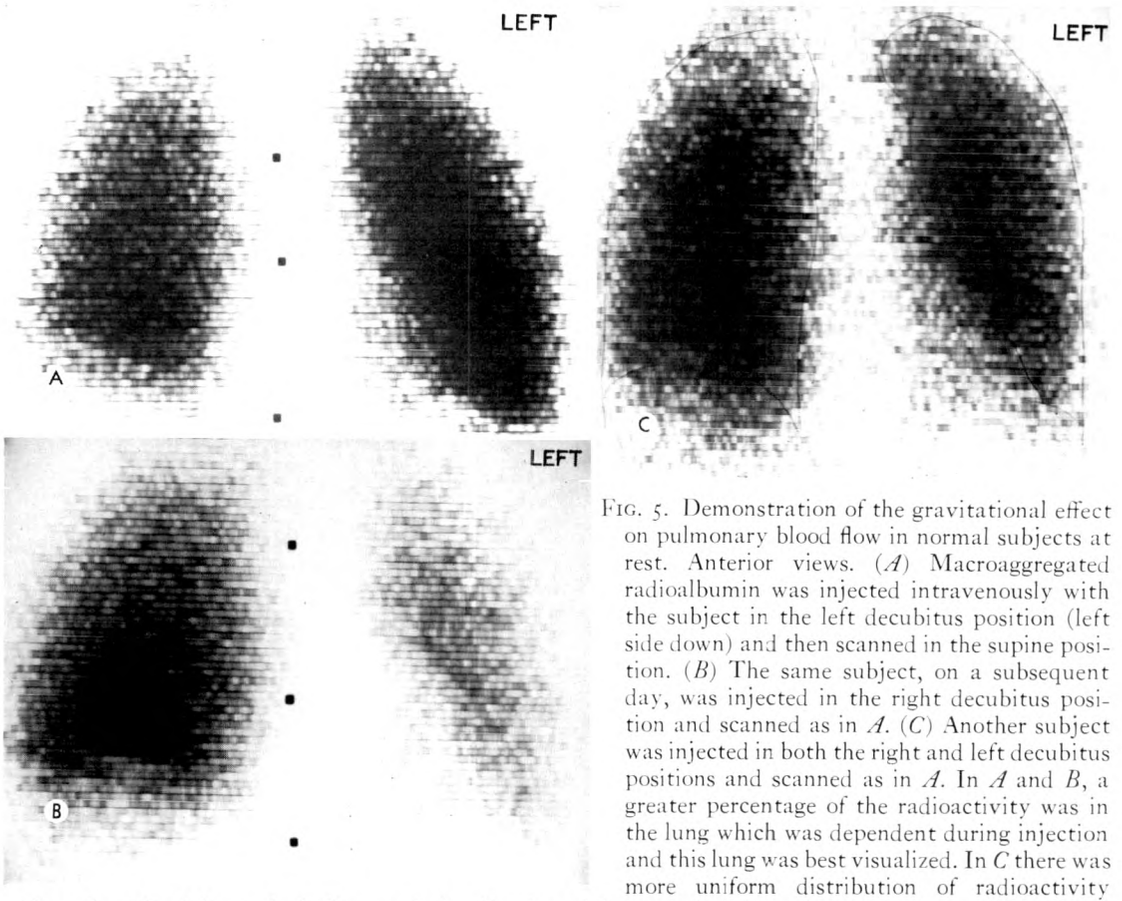


FIG. 5. Demonstration of the gravitational effect on pulmonary blood flow in normal subjects at rest. Anterior views. (*A*) Macroaggregated radioalbumin was injected intravenously with the subject in the left decubitus position (left side down) and then scanned in the supine position. (*B*) The same subject, on a subsequent day, was injected in the right decubitus position and scanned as in *A*. (*C*) Another subject was injected in both the right and left decubitus positions and scanned as in *A*. In *A* and *B*, a greater percentage of the radioactivity was in the lung which was dependent during injection and this lung was best visualized. In *C* there was more uniform distribution of radioactivity throughout both lungs, including good visualization of the costophrenic angles.

density of 0.31 gm./cc., appears to be an ideal lung substitute[3] since the calculated lung density is 0.32 gm./cc.

Studies were also obtained with the phantom man constructed by Jacobson and Knauer.[3] The cork "lungs" were replaced with dry oatmeal. To simulate macroaggregated radioalbumin distributed in the lung, this material was sprayed into the oatmeal, dried and placed in the phantom's lung cavities.

Anatomic structures identified on the photoscans were derived from: (1) phantom studies, (2) comparison of the photoscans with the roentgenograms obtained in the identical positions, and (3) comparison of the photoscans to diagnostic roentgenographic studies.

Descriptions of the physiologic variations in pulmonary blood flow which affect the photoscan image were based on studies reported in the literature and corroborated with pulmonary photoscans.

OBSERVATIONS

The focus of the 19 hole collimator and the absorption characteristics of lung tissue are such that little activity of the opposite lung reaches the crystal when the chest is scanned in the lateral position. Figure 2*A* demonstrates the isodose pattern obtained with the 19 hole collimator from a 1 cm. diameter source of I^{131} in the box lung phantom. The isodose patterns in air and in water are shown for comparison. By superimposing the "lung" isodose pattern on a decubitus chest roentgenogram (Fig. 2*B*), it is apparent that little activity penetrates from the distant lung to the scanner when the chest is viewed laterally. Phantom man

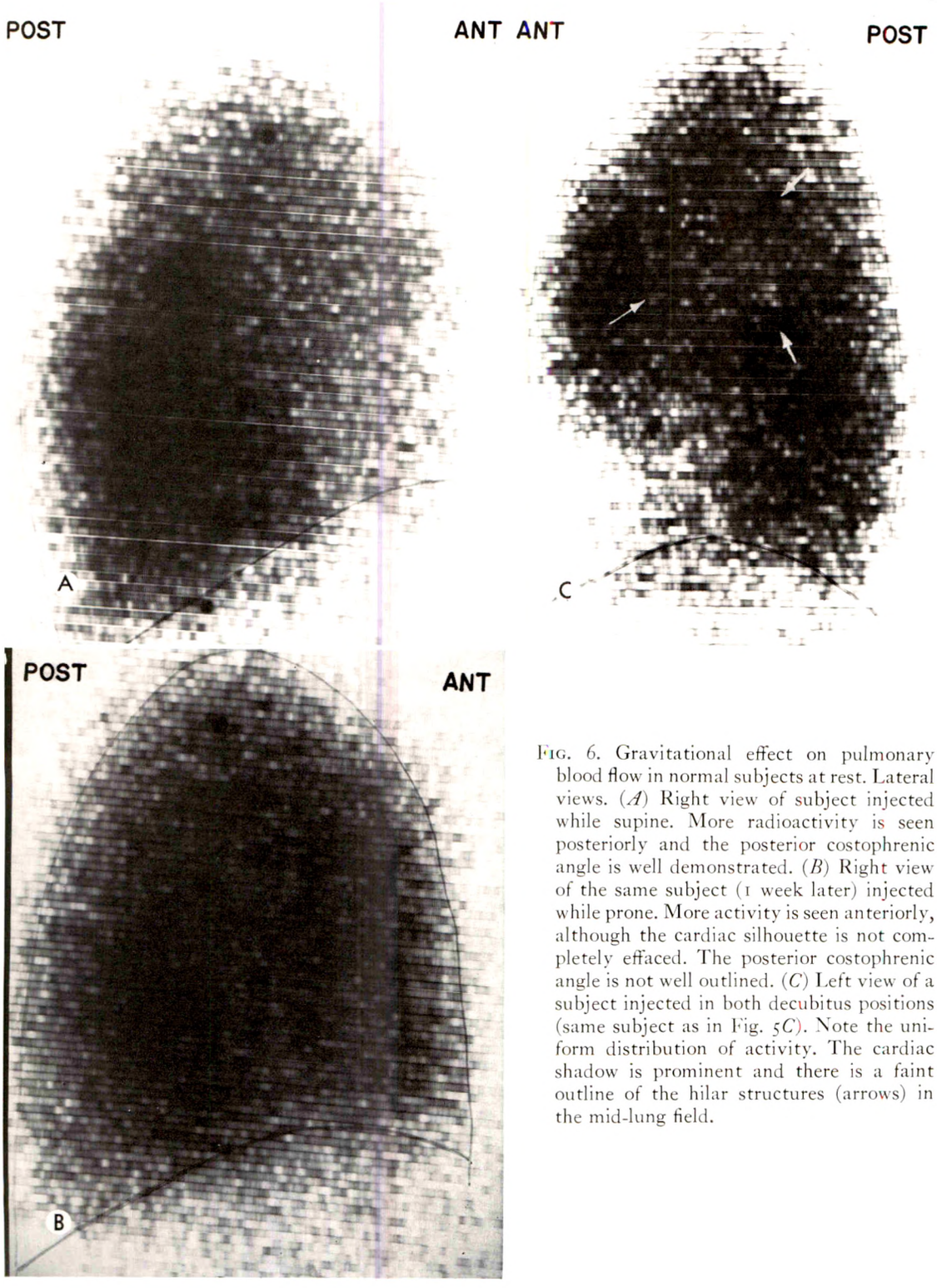


Fig. 6. Gravitational effect on pulmonary blood flow in normal subjects at rest. Lateral views. (*A*) Right view of subject injected while supine. More radioactivity is seen posteriorly and the posterior costophrenic angle is well demonstrated. (*B*) Right view of the same subject (1 week later) injected while prone. More activity is seen anteriorly, although the cardiac silhouette is not completely effaced. The posterior costophrenic angle is not well outlined. (*C*) Left view of a subject injected in both decubitus positions (same subject as in Fig. 5*C*). Note the uniform distribution of activity. The cardiac shadow is prominent and there is a faint outline of the hilar structures (arrows) in the mid-lung field.

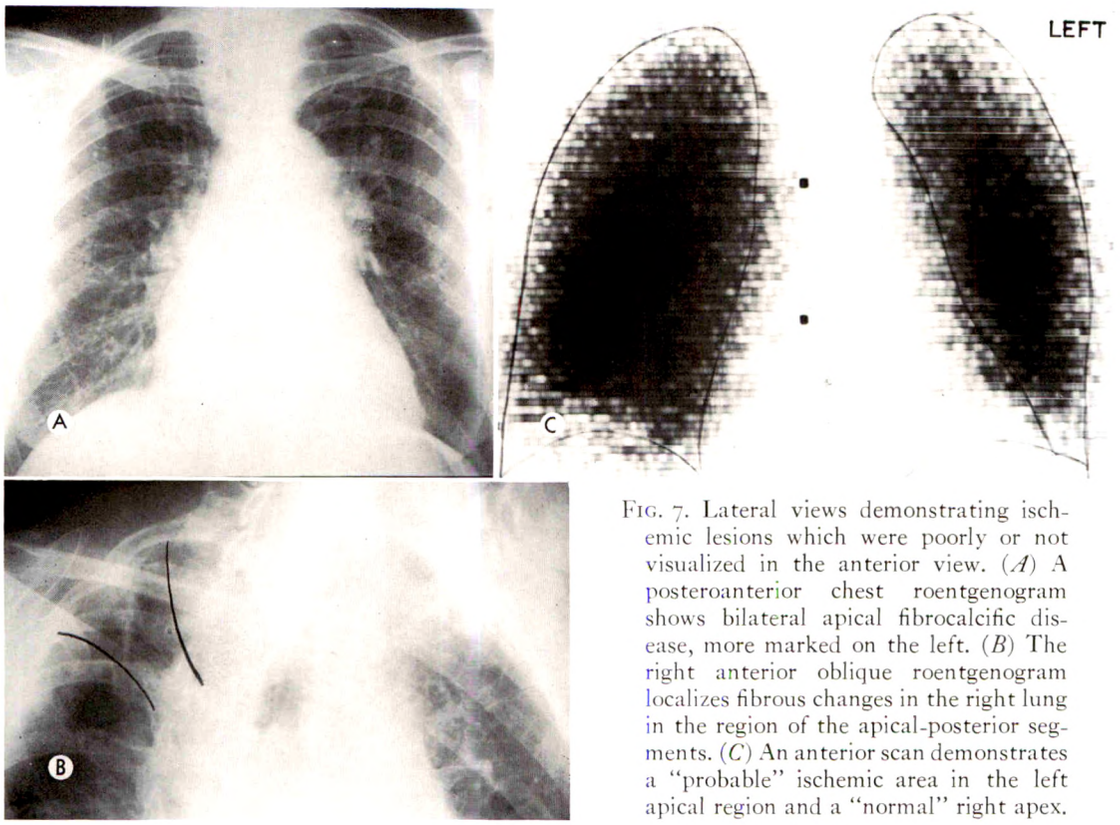


Fig. 7. Lateral views demonstrating ischemic lesions which were poorly or not visualized in the anterior view. (*A*) A posteroanterior chest roentgenogram shows bilateral apical fibrocalcific disease, more marked on the left. (*B*) The right anterior oblique roentgenogram localizes fibrous changes in the right lung in the region of the apical-posterior segments. (*C*) An anterior scan demonstrates a "probable" ischemic area in the left apical region and a "normal" right apex.

studies indicate that 15 to 30 per cent of the activity detected by the scanner comes from the distant lung. This was consistent with the findings in a patient with embolic occlusion of the left main pulmonary artery (Fig. 9, *A* and *B*). The proportion of activity contributed by the distant lung may be reduced by using a lower energy gamma emitter, *e.g.*, Tc^{99m}, and a more precise collimator.

The lateral decubitus position is desirable for lung scanning because the superior lung is expanded maximally and its hemidiaphragm is relatively immobile. Figure 3, *A* and *B* demonstrates the greater expansion of the left lung, in a subject lying on his right side, compared to the supine position. Occasionally, especially with obese or sick patients, we obtained better expansion of the superior lung in the decubitus position than was obtained in the upright inspiratory position used for diagnostic roentgenography. Further, the anteroposterior diameter of a lung is greater than its transverse diameter. In most patients, the total surface area of a lung seen by the scanner in the lateral projection is nearly double the surface area seen in the posterior projection. In the decubitus position, the elevated lung remains in the inspiratory position during the entire respiratory cycle.[5] These factors permit visualization of small ischemic areas.

The configuration of a lung scanned in the lateral projection approximates the shape of a mid-sagittal section. Structures consistently identified are the hemidiaphragm, which usually slopes upward anteriorly, and the cardiac outline on the left. The posterior costophrenic angle is usually well demonstrated (Fig. 6*A*). The heart may be seen in the right lateral view; in cardiomegaly it appears more prominent in both lateral views. Prominent hilar structures may be detected as light areas in the mid-lung field (Fig. 6*C*). A tortuous aorta may occasionally be detected. The spine and paraspinal muscles ordinarily cannot

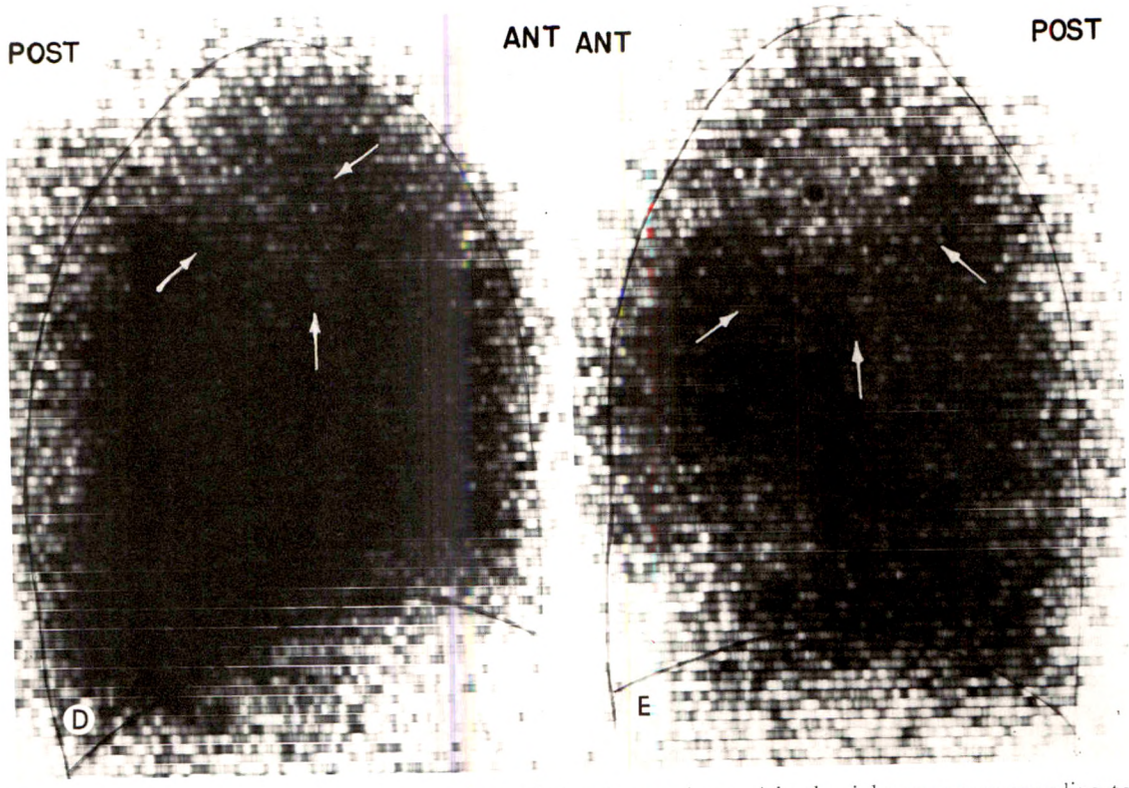


Fig. 7. (*D*) The right view shows a wedge shaped ischemic area (arrows) in the right apex corresponding to fibrosis (see *B*). (*E*) The left view confirms an ischemic process in the left apex (arrows) and more accurately defines the borders of the pathology. Note that although the subject was injected supine, the lateral views failed to show a gravitational effect (see Fig. 6*A*). This may reflect altered pulmonary blood flow secondary to the patients known borderline cardiac decompensation and/or the pulmonary fibrosis

be seen. Any of the mediastinal structures may be outlined if they are unusually prominent, if the subject is small or thin, or if a collimator with a distant focal point is employed. The photoscan image of mediastinal structures is enhanced since these structures absorb some of the activity emanating from the opposite lung. Thus the heart can usually be identified in the right lateral view. Pulmonary anatomy can be identified best with the aid of a roentgenogram of the chest obtained in the identical position as the scan. This is the most advantageous way of determining if the patient has been rotated (Fig. 4*A*) or if there is deformity of the chest such as pectus excavatum (Fig. 4*B*). It also reveals the exact location of the hemidiaphragm; the hemidiaphragm of the scanned (upper) lung is usually the most caudal (Fig. 3*B*).

The position of the subject during injection influences the distribution of the macroaggregated radioalbumin particles. The aggregates are uniformly distributed in the blood by the time they reach the main pulmonary artery. Areas of the lung receiving the most pulmonary blood have the greatest radioactivity. In resting subjects with normal pulmonary hemodynamics (pressure and flow), the blood flow is greatest in the dependent segment. This was suggested by Rodbard[4] with a model constructed to simulate the pulmonary vascular system. Increasing the "pre-capillary" resistance in this model (simulating pulmonary hypertension) resulted in equalizing the flow between the superior and dependent vessels. Raising "left atrial" pressure (simulating mitral stenosis or left ventricular failure) also equalized the flow. That this occurs in man has been confirmed by Dollery *et al.*[2] They demonstrated that

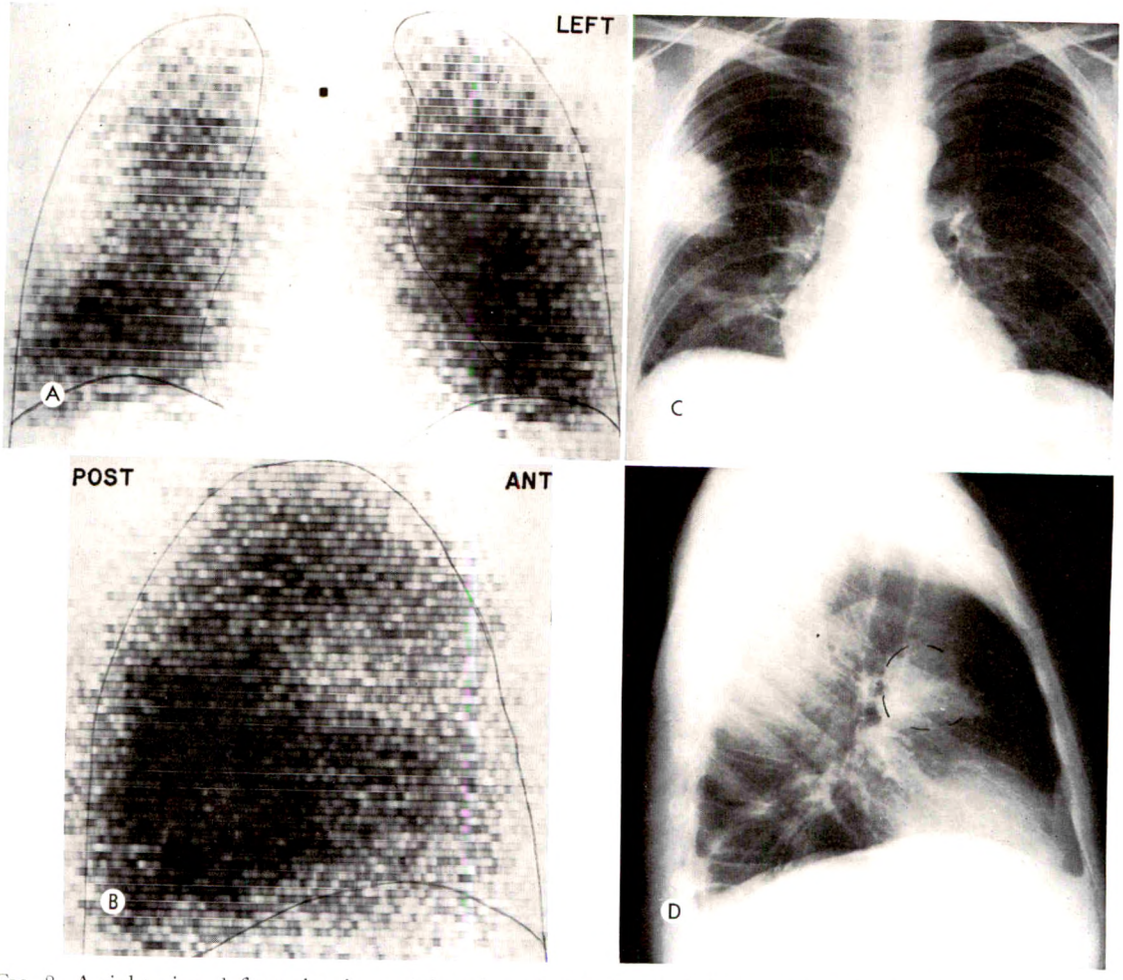


Fig. 8. A right view defines the size and location of an ischemic lesion seen in the anterior view. (*A*) An ischemic area is seen in the lateral aspect of the right lung in the anterior view. The upper margin of the lesion is not distinct nor can one be sure if the lesion is in the upper and/or lower lobe. (*B*) Right view clearly outlines the ischemic process as being in the anterior segment of the upper lobe. (*C* and *D*) Roentgenograms confirm the location of the ischemic lesion.

while blood flow per unit lung was greatest in the dependent vessels in normal subjects, it was nearly equal in the dependent and superior vessels in patients with mitral stenosis,[1] congestive heart failure[8] or congenital heart defects who had either pulmonary hypertension or increased pulmonary blood flow without hypertension.[2] Pulmonary photoscans demonstrated the effect of gravity on pulmonary blood flow distribution in normal subjects. Figure 5, *A*, *B* and *C* shows a greater concentration of activity in the left lung in a normal subject injected while lying on the left side, in the right lung when injected lying on the right side, and uniform distribution across both lungs when a half-dose was given another normal subject lying on either side. In Figure 6*A* a normal subject was injected supine, producing the greatest concentration of activity posteriorly; later (Fig. 6*B*), he was injected prone, producing greater activity anteriorly. It is frequently observed in anterior scans that the lower left lung and the right costophrenic angles are faintly visualized. In our experience this has been so, especially when the subject is supine during injection. However, such areas can be optimally demonstrated if the gravitational principle is utilized, *i.e.*, injecting the sub-

ject prone or while lying on his side (Fig. 5, *A*, *B* and *C*). As previously indicated, the gravitational effect is minimal in subjects with elevated pulmonary vascular pressure or flow so that uniform distribution to the entire vascularized lung can be expected in subjects with altered pulmonary hemodynamics (Fig. 7, *A–E*).

The lateral lung scan offers several other advantages. Frequently, postoperative patients or those with respiratory distress cannot lie prone, the position used for posterior views with most commercial scanners. Lateral views can generally be obtained in these patients, and in this way the posterior lung can be visualized. Small lesions may be detected on the lateral view which cannot be seen on the anterior or posterior views (Fig. 7, *A–E*). The location, size and shape of an avascular lesion seen on an anterior and/or posterior view can be more accurately defined with the aid of the lateral view (Fig. 8, *A–D*). Comparison of the lateral photoscans with the anterior and/or posterior views, especially with the aid of roentgenograms, frequently permits precise identification of the lung segment(s) involved by an ischemic process (Fig. 9, *A* and *B*).

COMMENTS

Like the lateral chest roentgenogram, the lateral lung photoscan may at first be confusing to the uninitiated observer. As the new physician learns to evaluate the shadows on a lateral chest roentgenogram, he soon finds that as much information can be gained from this view as from the postero-anterior view, and that actually both projections are necessary for an adequate roentgenographic examination of the chest. Similarly, it appears that lateral photoscans, in addition to either the anterior or posterior view (preferably both), may be necessary for an adequate photoscanning examination of the lungs. As we gain experience with multiple views and as scanning techniques are improved, the lateral views may prove to be the most useful projections.

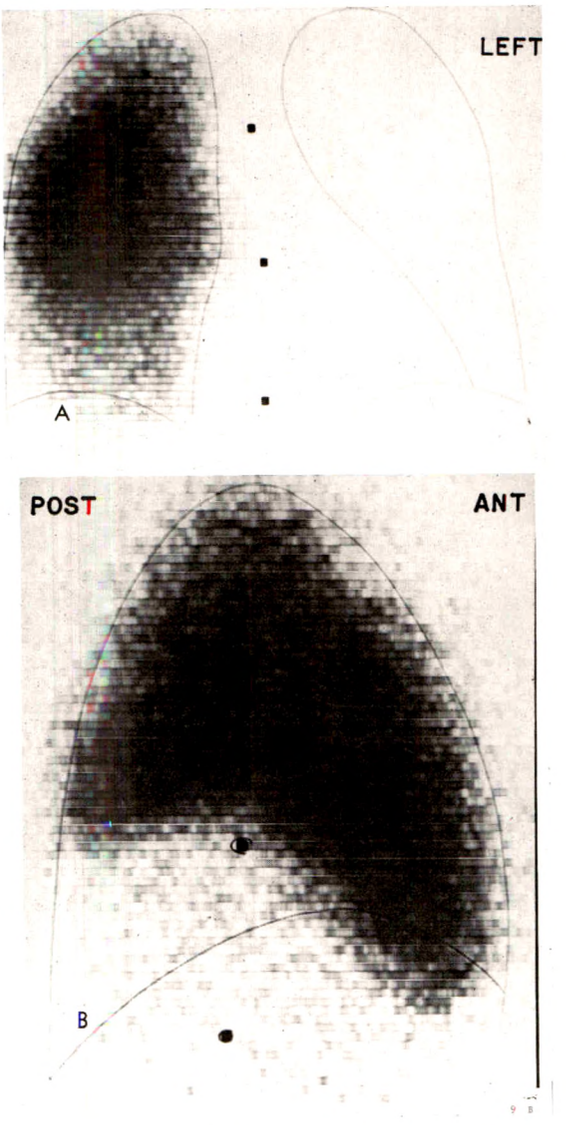


Fig. 9. Exact delineation of ischemic pulmonary segments in a patient with multiple pulmonary emboli. The segmental pulmonary arteries involved by pulmonary emboli were inferred preoperatively by identification of the ischemic lung segments. (*A*) Anterior view shows almost complete ischemia of the left lung and a portion of the "right lower lung field." (*B*) The right view shows that the ischemic "right lower lung field" is limited to the right lower lobe, except in its superior segment.

At present, we feel that there is no "best" position for the subject during injection of the macroaggregated radioalbumin. Generally, we use the supine position since this is most convenient, especially in critically ill

patients. Occasionally, if we wish to demonstrate a particular segment of the lung, we will position the subject so that this segment is most dependent during injection. In patients with significant cardiac or pulmonary disease, the position may have no effect. The accurate interpretation of lung photoscans will require a better understanding of the normal and pathologic-physiologic mechanisms which determine distribution of pulmonary blood.

SUMMARY AND CONCLUSION

A lateral scan of the chest visualizes the lung closest to the detector.

The lateral decubitus position permits maximum expansion of the superior (scanned) lung with little respiratory motion of its hemidiaphragm.

The configuration of a lung scanned in a lateral projection approximates the shape of a mid-sagittal section through that lung. Prominent mediastinal structures may be outlined.

Roentgenograms of the chest should be obtained with the subject in the scanning position; the hemidiaphragm of the scanned (superior) lung will usually be most caudal.

The position of the subject during injection will influence the distribution of the macroaggregated radioalbumin except in subjects with increased pulmonary vascular pressure or flow.

The lateral view permits visualization of posterior basal lung segments in subjects who are unable to lie prone for a posterior view.

Small lesions not demonstrated in the anterior or posterior view may be detected in the lateral view.

The lateral view permits better definition of the size and shape of lesions seen on the anterior or posterior view; frequently, the specific lung segment(s) involved by the pathologic process can be identified.

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I wish to thank the many members of the Department of Radiology, U.C.L.A., who assisted in this study. I am particularly indebted to Dr. Leslie R. Bennett for his many helpful suggestions and his encouragement.

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SELECTIVE CINEBRONCHOGRAPHY IN OBSTRUCTIVE AND RESTRICTIVE PULMONARY DISEASE*

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DURING the past several years, we have supplemented all bronchographic examinations with cinefluorography in addition to the conventional spot film and erect roentgenography. Soon after the institution of this program, it became clear that there is much useful information, often of critical importance, which the cinefluorograms alone can yield, while it either remains ambiguous or cannot at all be extracted from conventional bronchograms. In general, the minimum cine sequence consists of recording several respiratory cycles during the filling of each lobe followed by observation of various areas of the tracheobronchial tree during deep respiration and, after removal of the catheter and preferably in the erect position, of the peripheral bronchi, central bronchi and trachea during forceful voluntary cough. A fairly large body of cinebronchograms has thus been created and has been correlated with clinical and spirometric findings.

All bronchograms are obtained under fluoroscopic guidance by peroral passage of radiopaque tapered rubber catheters (either Bardam-Thompson* or Metras†) with appropriate tip curvatures and central end hole. Meticulous topical analgesia facilitates maximal patient cooperation and also assures continuous positive control of the catheter for the deliberate selective opacification of specific lobes or segments. All bronchographies to date have been performed with Hytrast‡ without any serious complications.

* Bardam-Thompson Bronchial Catheter, C. R. Bard, Inc., Murray Hill, N. J.

† Metras Bronchographic Catheter, Etablissements G. Guichard, 141 Bvd. Sevastopol, Paris (2ème), France.

‡ Iopydone-Iopydol, E. Fougera & Co., Inc. Production of this contrast medium has, unfortunately, been discontinued.

TABLE I

CLASSIFICATION OF VENTILATORY DYSFUNCTIONS

A. *Restrictive: Increased stiffness of respiratory apparatus*
   1. Bellows: decreased amplitude of excursion
      (a) Chest wall (example: Marie-Strümpell spondylitis)
      (b) Pleura (example: pneumothorax)
   2. Lungs: decreased compliance or elasticity (example: interstitial fibrosis)

B. *Obstructive: Increased resistance to airflow*
   1. Local or general
   2. Inspiratory and/or expiratory
   3. Acute or chronic
   4. Various levels of tracheobronchial tree

The patients originate from the various services of a large, adult, general university hospital, and are predominantly referred for establishment of a diagnosis rather than mere documentation of a diagnosis already made by other means. Thus, there is a high incidence of genuine problems of bronchopulmonary diagnosis. Among these, the study of bronchopulmonary function by cinefluorography has been most rewarding, to date, in cases with ventilatory disorders. A practical classification of these conditions is presented in Table I.

The author proposes to illustrate the unique contributions of cine studies to the recognition and understanding of abnormal bronchopulmonary dynamics in several categories of ventilatory disturbances. In each case, findings of functional rather than anatomic significance are emphasized, cinefluorographic diagnostic criteria developed, and their illustration by still photographic prints attempted. Admittedly, still prints of moving picture frames cannot convey the dynamic impact of direct analysis of the

* Presented at the Fourteenth Annual Meeting of the Association of University Radiologists, Little Rock, Arkansas, May 12–14, 1966.

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original. Parallel enlarged photographs* of three consecutive cineframes showing comparable inspiratory and expiratory sequences are therefore reproduced in the belief, based on considerable experimentation, that this represents the optimal compromise available for such documentation.

DEFINITIONS

For the sake of clarity during the ensuing presentation, the following terms require definition according to the manner in which they should be employed, in the author's opinion, by radiologists. Indeed, widely divergent interpretations of these terms have been encountered.

1. *Chronic bronchitis* means, exactly, chronic inflammatory involvement of bronchial walls. This is a well known and clearly definable pathologic entity[12] affecting one or more layers of bronchi and consisting of collections of chronic inflammatory cells, microabscesses, fibroblastic infiltration, mural edema, epithelial degeneration, ectatic bronchial mucous glands, thickened mucous gland ducts, bronchiolar ectasia, and excessive, usually purulent, mucus secretion. All or any of these may appear in various combinations producing the radiographic features of chronic bronchitis which have been well described and documented, in particular by Freimanis and Molnar[6] and Rayl *et al.*[10] It must be noted that the pathologic lesions occur in a patchy discontinuous manner with areas of greater and lesser involvement alternating with more or less normal tissues along both the long and circumferential dimensions. The usual clinical definition of "chronic productive cough" does not lend itself to precise roentgen diagnosis.

2. *Bronchiectasis* is also a clearly pathologic diagnosis, characterized by gross deformity and dilatation of bronchi, by gross destruction of bronchial muscle and elastic tissue (and, late, of other components as well) and replacement of mural components by fibrous and granulation tissue. Any and all features of chronic bronchitis may also be present. The differential roentgen diagnosis of bronchiectasis and bronchitis has been well discussed by Rayl *et al.*[10] and basically rests on an estimate of degree of rigidity and of magnitude of the deformities.

3. *Broncho- or tracheomalacia* as used hereafter implies a significant loss of resistance to deforming forces and in particular to the effect of increased intrathoracic pressure upon a structurally damaged bronchus. This is simply a descriptive term relating to tracheobronchial dynamics regardless of the etiologic mechanism involved, and literally means "soft" or "mushy."

4. *Obstructive emphysema* is the comprehensive name of those conditions of altered pulmonary physiology characterized by increased expiratory airflow resistance. It is a functional entity diagnosable by physical signs, subjective symptoms, spirometric measurements, and roentgen findings. The pure pathologic definition ("destruction of alveolar septa") does not lend itself to roentgen diagnosis nor to radiologic differentiation from other conditions having similar respiratory impairment and increased radiolucency of the lungs as indicated by Fleischner[4] and many others; nor are the mere roentgen findings of hyperinflated lungs, increased diameter of the chest, etc. sufficient to warrant the diagnosis of obstructive emphysema. Evidence of actual air trapping is the key to the recognition of this condition.

REPRESENTATIVE CASES

A. NORMAL BRONCHOPULMONARY DYNAMICS

The normal bronchogram (Fig. 1, *A* and *B*) is characterized by even and progressive centrifugal tapering of bronchial caliber, even and proportionate pattern of contraction and expansion of the bronchi centrally and peripherally during the respiratory cycle, smooth flexibility of the bronchi with respiration, orderly progression of opacification and uniform distribution of contrast medium instilled into lobar or

* Each original strip of 16 mm. cine frames is copied on a Leitz Macrostand® onto a 4×5 inch sheet of Tri-X film.® The negatives are then enlarged on Kodabromide® paper of appropriate contrast. The photography was performed by Mr. David L. Brittain of the Department of Medical Illustration of the University of Pittsburgh.

segmental orifices, regular peripheral distribution of the smaller bronchi, indirect evidence of normal pulmonary compliance by the regularity and proportionality of displacement of the filled bronchi by the moving lung during respiration, and the regular and uniform flow of air in and out of the peripheral lung shown by air bubbles traversing intraluminal collections of contrast medium.

B. RESTRICTIVE DEFECTS OF VENTILATION

1. *Rigidity of "bellows"* is illustrated by a case of left thoracoplasty (Fig. 2, *A* and *B*). The abscessed atretic residue of the left bronchial tree is rigid and moves only *en bloc* with the surrounding, airless, fibrothorax. There is no variation of bronchial caliber or configuration and no evidence of air exchange during respiration.

2. *Stiffness of lung tissue* ("loss of compliance") precludes adequate ventilation. Figure 3, *A* and *B* shows fibrosis of the anterior segment of the right upper lobe and of the entire right middle lobe resulting from radiation therapy for carcinoma of the right breast. The affected bronchi fail to expand during inspiration, move only slightly, *en bloc*, with the surrounding lung but are fixed with respect to one another in contrast to the normal bronchi in adjacent fields which expand during inspiration and show normal mobility and elasticity during the respiratory cycle. There is little or no airflow from the affected portions of lung. It is interesting that conventional chest roentgenograms demonstrate no gross parenchymal involvement. Bronchography was performed because of hemoptysis.

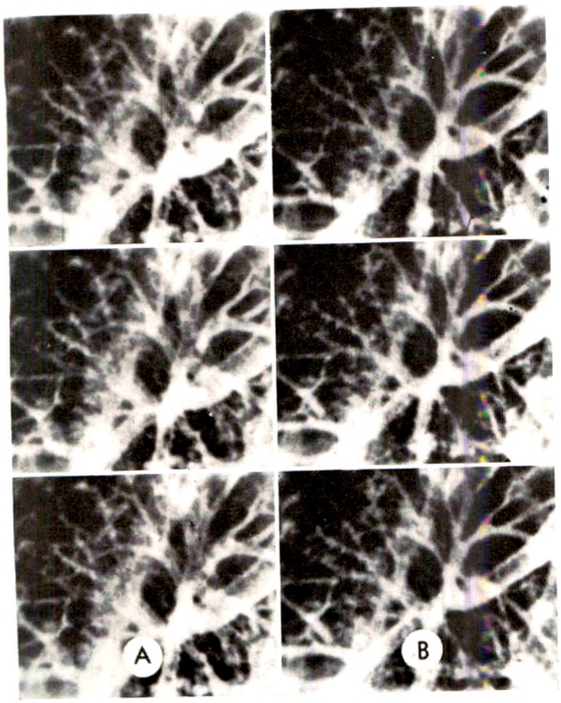


Fig. 1. Normal dynamics of left upper lobe filling. (*A*) Inspiration. (*B*) Expiration.

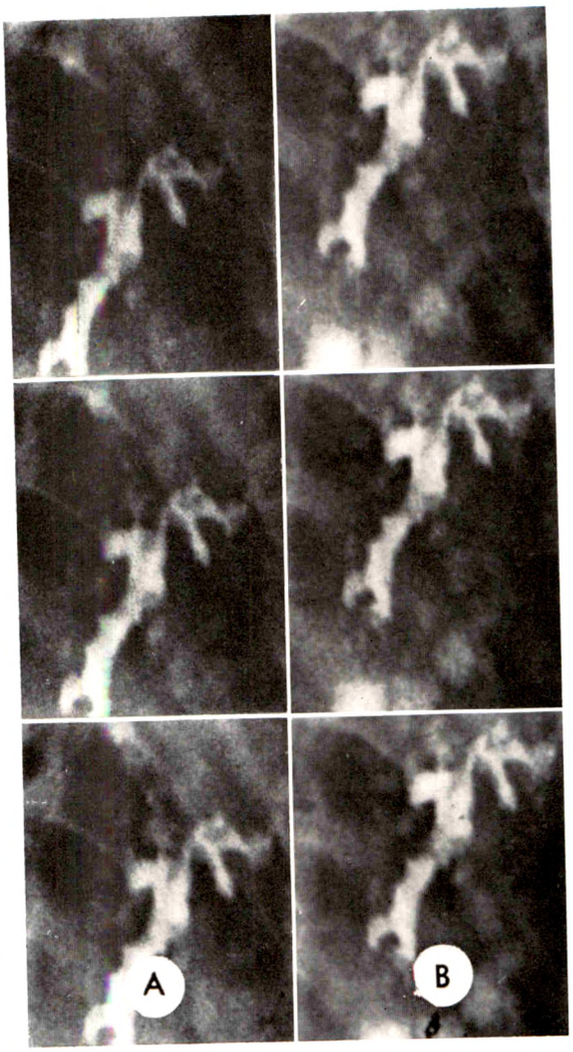


Fig. 2. Rigidity of bellows (left thoracoplasty). Saccular remnants of bronchial tree are encased in rigid fibrothorax. (*A*) Inspiration. (*B*) Expiration.

3. *Replacement of functioning elastic lung tissue* by emphysematous bullae (Fig. 4,

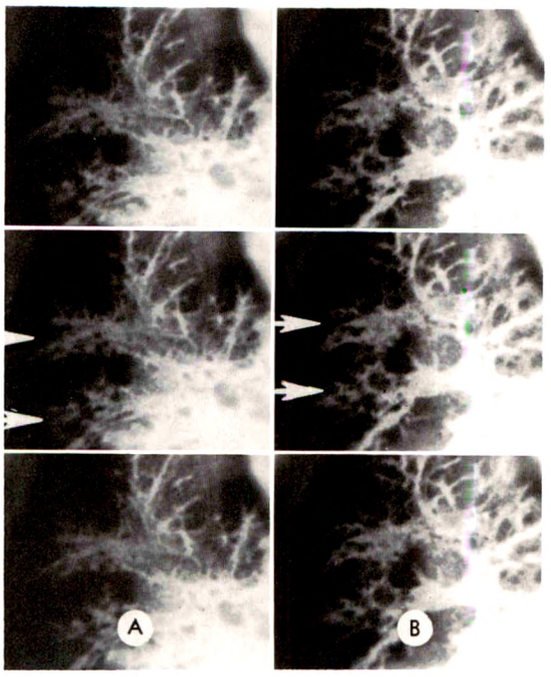


Fig. 3. Localized loss of compliance secondary to parenchymal (postirradiation) fibrosis (anterior segment of right upper lobe and right middle lobe). The affected tissue is fixed, cannot expand during inspiration, and is not ventilated. (*A*) Inspiration. (*B*) Expiration.

A and *B*) also impairs compliance. The bullae compress and stretch the bronchi. The compression is roughly equal peripherally and centrally and is most notable during expiration. The bronchi adjacent to bullae are stiff and thin. The airflow pattern shows minimal progression of air bubbles peripherally during inspiration and minimal return proximally during expiration, indicating severely deficient ventilation.

C. Acute, Generalized Airway Obstruction

A sudden episode of acute bronchial asthma occurred during bronchography of a 42 year old white female with multiple allergies, chronic bronchitis and excessive sputum production, suspected of bronchiectasis (Fig. 5, *A* and *B*). There is massive peripheral trapping of air, expulsion of contrast medium from intermediate bronchi during expiration by extrinsic compression, ineffective expiratory effort and the well known prolongation of the expiratory phase. In addition, the cinefluorogram demonstrates multiple areas of transitory focal spasm along many bronchi of medium and smaller sizes, more severe during expiration, persisting through several respiratory cycles, and finally eliminated by the intravenous administration of aminophylline coincident with symptomatic relief. It is hardly surprising that the intermediate order bronchi participate in the generalized bronchospasm but, because this event has not been convincingly demonstrated hitherto, it has been thought, by many, not to occur.

D. Chronic Generalized Expiratory Airway Obstruction: Chronic Obstructive Emphysema

1. *Pure chronic obstructive emphysema* is generally thought to result from stenosis at the level of the terminal bronchioles or

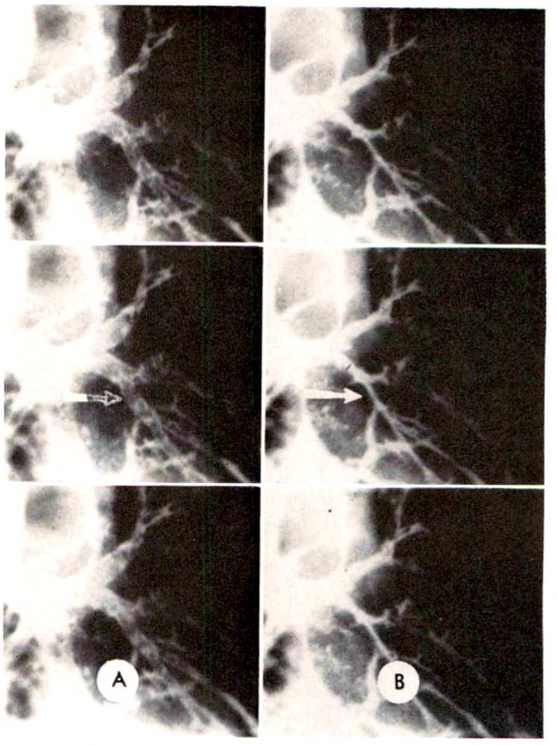


Fig. 4. Generalized loss of compliance secondary to extensive bullous emphysema. The lungs are rigidly expanded and cannot be well ventilated. Bullae compress the bronchi during expiration. (*A*) Inspiration. (*B*) Cough.

alveolar ducts. Figure 6, *A* and *B* illustrates such a case. Like a pneumatic cushion, the trapped air mass acts as if to resist penetration by contrast medium and the diffusely overinflated peripheral pulmonary parenchyma compresses the bronchi and squeezes the contrast medium contained within them centrally during expiration. With inspiration, contrast medium progresses peripherally by small distances, only to be repelled again during the following expiration. Rarely if at all are the smaller bronchi filled. Only a small amount of air moves during each respiratory cycle, an indication of the profound impairment of ventilation. In the present case of presumably purely bronchiolar stenosis there are no visible areas of bronchial buckling

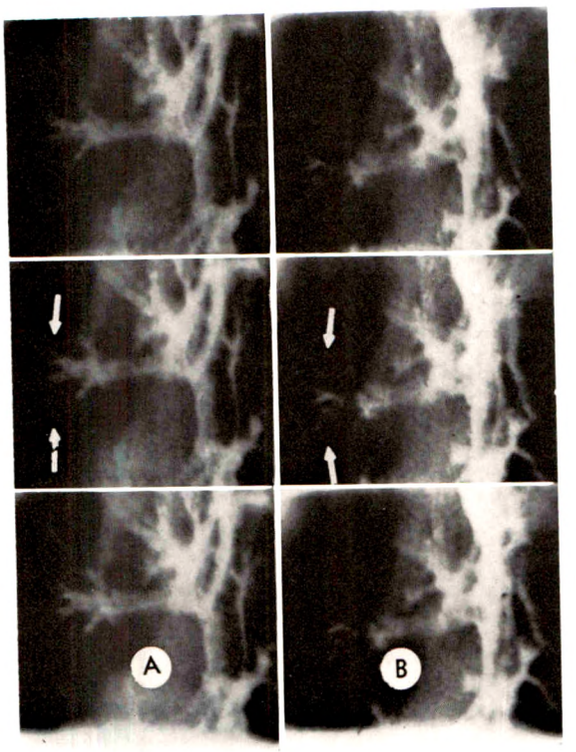


Fig. 6. Severe pulmonary obstructive emphysema *without* bronchomalacia. Contrast medium is squeezed out of the bronchi during expiration. Peripheral bronchi cannot be filled. Air trapped peripherally acts like pneumatic cushion. Scalloping of bronchi indicates severe chronic bronchitis, but no areas of expiratory buckling are seen. Stenosing mechanism, presumably, occurs at peripheral bronchioles. (*A*) Inspiration. (*B*) Cough.

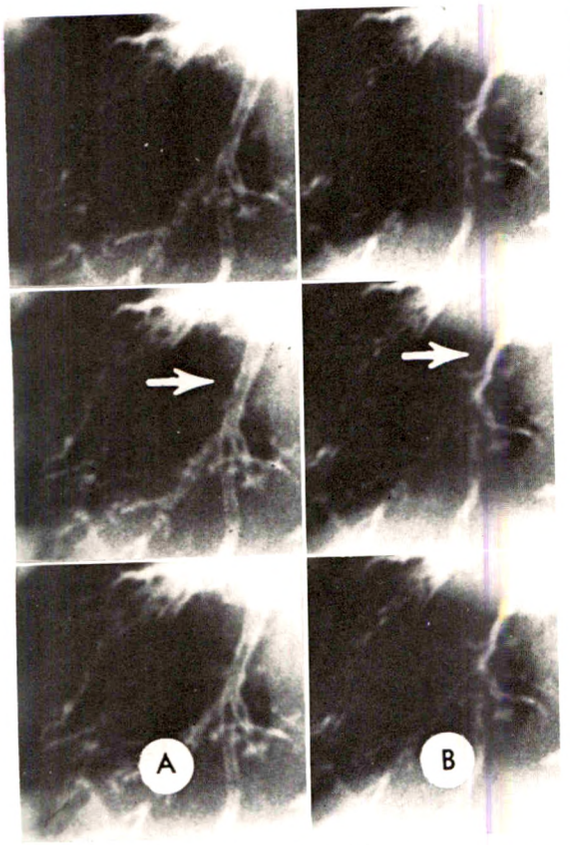


Fig. 5. Acute bronchial asthma. Transitory bronchospasm of a segmental bronchus (posterior basilar segment of right lower lobe). Occlusion is more marked in expiration than in inspiration. (*A*) Inspiration. (*B*) Expiration.

(malacia) or spasm. The opacified bronchi show changes of chronic bronchitis, but other equally severe cases are seen free of stigmata of chronic bronchitis. Because of the overexpansion of the chest and the trapped air in the lung, all opacified bronchi are stretched and strikingly straight throughout the respiratory cycle, and branch at sharp angles. The trachea and large bronchi widen during inspiration much beyond normal dimensions to permit maximal inflow of air, and may or may not remain widely patent during expiration and cough depending on their structural characteristics and on the relative magnitude of intrathoracic and intraluminal pressures which oppose each other transmurally. With increasing duration of the disease, the

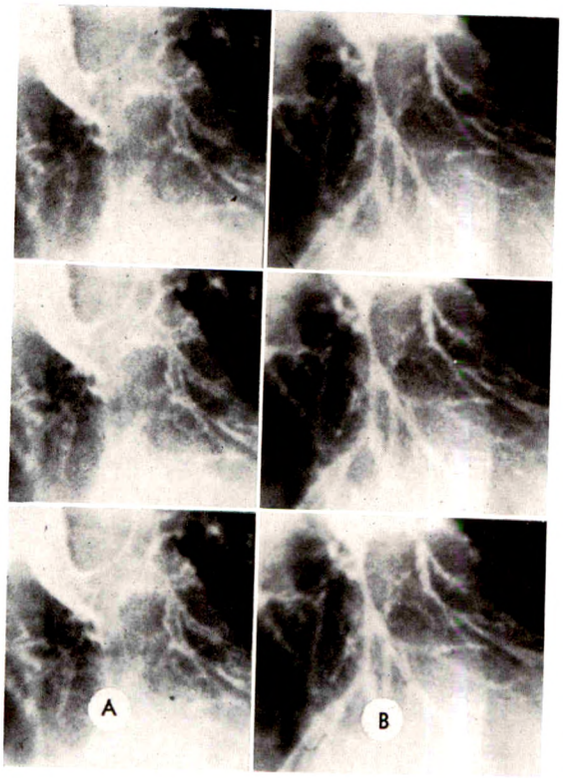


Fig. 7. Severe pulmonary obstructive emphysema *with* focal bronchomalacia. Peripheral bronchi are quite adequately filled despite severe air trapping. Ectatic mucous glands, scalloped bronchial walls, and other findings not reproduced here indicate advanced chronic bronchitis. During expiration, many bronchi of intermediate size buckle and occlude the lumen. This occurs most conspicuously in those areas which exhibit the most pronounced roentgen changes of bronchitis, suggesting the etiologic role of focal damage of bronchial walls. (*A*) Inspiration. (*B*) Cough.

major airways tend to remain fixed at their maximal caliber despite occasional severe buckling of the trachea during violent coughing in individuals with long standing chronic bronchitis.

2. *Focal malacia of intermediate order bronchi associated with evidence of severe chronic bronchitis* (Fig. 7, *A* and *B*) is often seen in cases which fulfill all clinical and spirometric criteria of chronic obstructive pulmonary emphysema. As in the preceding case, there is conspicuous overdistention of the lung and compression of the bronchi by trapped peripheral air but the pneumatic cushion effect is lacking, permitting better propagation of contrast medium and improved opacification of the bronchial tree. During inspiration, while limited inflow of air is evidence of impaired ventilation, contrast medium advances quite readily once it has passed the level of lobar and major segmental bronchi. The essential, fundamental phenomenon, however, only occurs during active expiration and cough. It consists of a striking, albeit transient, degree of focal buckling, narrowing or kinking of certain intermediate order bronchi, usually in those areas with the most marked features of chronic bronchitis. It seems entirely plausible that the characteristically nonuniform distribution of mural infiltrates in chronic bronchitis (see section on "Definitions" above) damages the bronchi structurally by varying

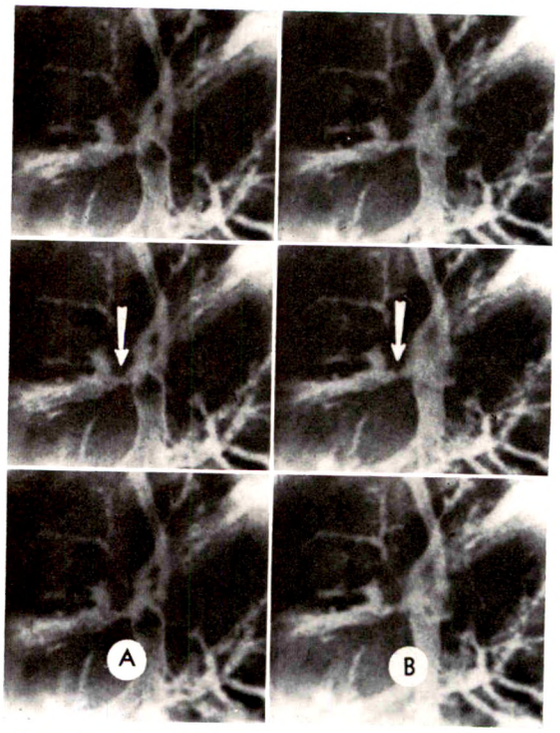


Fig. 8. Segmental atelectasis and bronchiectasis distal to focal bronchomalacia (anterior segment of right upper lobe). The bronchus proximal to the stenosis appears normal, although the patient has clinical and roentgen findings of chronic bronchitis. The stenotic lesion distends during inspiration, hence is considered as an area of bronchomalacia rather than a fibrous stricture. (*A*) Inspiration. (*B*) Expiration.

degrees along both longitudinal and circumferential dimensions. This predisposes to buckling under the impact of brisk increases of expiratory intrathoracic pressures. Inherent to the nature of this event is the fact that it can *only* be demonstrated dynamically while it actually occurs, and not while the patient holds his breath nor in the pathologic specimen after surgery or autopsy. Cases of this type also illustrate many other essential contributions of cinefluorography in chronic bronchitis which will be more fully discussed below. Of interest is the fact that many such patients have regional or localized rather than diffuse emphysema. This is readily shown by cine studies, but is often unclear clinically or spirometrically.

E. LOCALIZED AIRFLOW OBSTRUCTION

1. *Segmental atelectasis and bronchiectasis distal to focal bronchomalacia* is illustrated in Figure 8, *A* and *B*, in the anterior segment of the right upper lobe of a patient with extensive chronic bronchitis. This stenosis is nearly total during expiration or cough but expands partially during inspiration, hence the lesion is considered as a soft area of damaged buckling bronchial wall rather than as a fixed fibrous stenotic ring. Despite absence of airflow to or from this diseased segment, the stenosis expands sufficiently during inspiration to permit the inflow of contrast medium, hence its mechanical significance escapes recognition on conventional roentgenograms. The stricture is short, the bronchus proximal to the stricture is grossly intact, and there are marked changes of chronic bronchitis elsewhere. It is, therefore, logical to suggest that focal damage, either inflammatory or traumatic, of the segmental bronchial wall antedated the distal disease, causing expiratory obstruction, retention of air and secretions, gradual breakdown of distal subsegmental bronchial walls, and finally loss of function coincident with permanent atelectasis and bronchiectasis.

2. *Focal lobar bronchomalacia considered to be of mechanical etiology* is shown in Figure 9, *A* and *B*. Chronic mechanical stresses may damage bronchial walls in a nonuniform fashion, or apply nonuniform forces to a bronchus of basically uniform structure. Here again, there may result focal bronchomalacia characterized bronchographically by expiratory kinking or buckling which can only be recognized

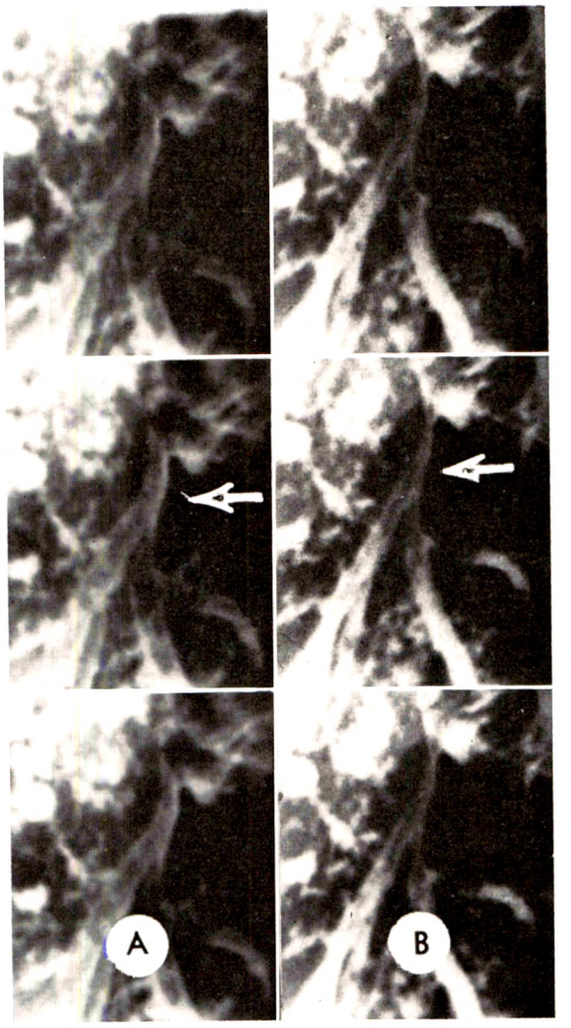


Fig. 9. Lobar bronchomalacia (right middle lobe), believed adaptive in etiology because of mechanical stresses following right lower lobectomy for bronchiectasis 2 years previously. The right middle lobe was normal at that time. Now, the lobar bronchus is soft and becomes nearly occluded by buckling during expiration and coughing. Airflow through it is reduced. Secretions are trapped beyond it and the peripheral bronchi definitely are bronchiectatic. (*A*) Inspiration. (*B*) Cough. Note normal stump of right lower lobe.

while air is actually expelled from the periphery. Obviously, this phenomenon is not detectable during inspiration or when the patient holds his breath, hence it cannot be seen on conventional roentgenograms because the rapid visual sequence of respiratory events is lost. Illustrated here is the case of an otherwise healthy 37 year old man whose right lower lobe had been removed 2 years previously for bronchiectasis. The bronchial stump seen here is not remarkable. At that time, the right middle lobe appeared normal both during bronchography and by direct inspection during surgery. It was, therefore, not resected. Wheezing, air trapping and rales at the right base soon recurred and again became disabling. The current cinebronchogram demonstrates that during inspiration (Fig. 9*A*) the right middle lobe bronchus is long and patent, but becomes partially occluded at its origin by buckling during expiration and coughing (Fig. 9*B*), causing retention of air and secretions distally where there is now well established cylindrical bronchiectasis. Airflow to and from the middle lobe is severely reduced. Following right middle lobectomy the patient experienced gradual remission of his respiratory disability and is now considered cured. The pathologist described the bronchus as "irregularly thick, soft and mushy" and the peripheral bronchiectasis was confirmed. The histologic changes of bronchiectasis (fibrosis and chronic inflammatory reaction) also extended into the lobar bronchus to some degree. The chronology of evolution of this case, together with the elongated appearance during inspiration, the cinebronchographic evidence of expiratory kinking of the lobar bronchus and the marked changes of its caliber during the respiratory cycle (there is not sufficient rigidity to justify the diagnosis of gross bronchiectasis) suggest that the distal bronchiectasis resulted from the adaptive elongation and expiratory occlusion of the middle lobe bronchus secondary to right lower lobectomy, rather than the inverse.

3. *Post-traumatic or postoperative areas of softening*, best seen during expiration and coughing and not strikingly abnormal during inspiration may occur at any level of the tracheobronchial tree. Figure 10, *A* and *B* shows the tracheogram of a 54 year old male with dyspnea and "obstructive emphysema" first noticed upon recovery, 6 months previously, from a depressed fracture of the upper sternum incurred during a steering wheel injury. The sternum was repaired surgically while a long tracheostomy tube, by fortunate coincidence, bridged an unrecognized concomitant tracheal frac-

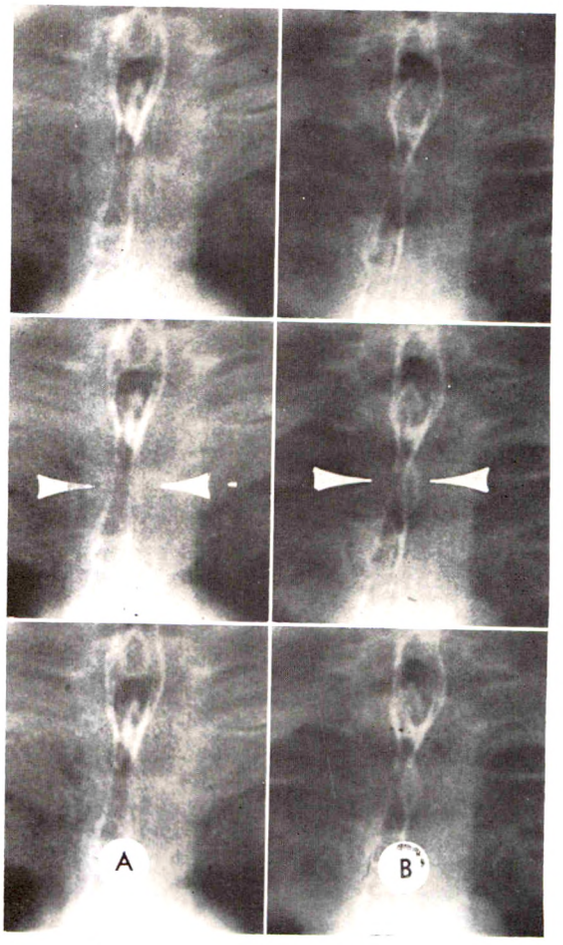


Fig. 10. Post-traumatic focal tracheomalacia. Functionally negligible during inspiration, this lesion impedes expiratory airflow significantly during expiration so as to resemble conventional chronic obstructive emphysema. (*A*) Inspiration. (*B*) Early phase of cough. Absence of subglottic distention indicates that expiratory air pressure is not transmitted through stenosis.

ture. There is only moderate and asymptomatic constriction of the trachea during inspiration, but significant buckling during coughing at the level of the fracture. Expiratory airflow, as estimated by the propulsion of airway contents such as contrast medium and/or mucus during expiration, is normal below the stricture but grossly diminished above the stricture. Normally, the initial phase of coughing occurs against the closed glottis and is attended by marked subglottic distention prior to release of the vocal cords. In the present case, this distention does not take place, indicating that insufficient expiratory air pressure is transmitted across the stricture into the subglottic space. The cinebronchogram is entirely normal in every other respect, especially in regard to evidences of peripheral pulmonary emphysema. The etiology of expiratory air trapping is therefore attributed to the tracheal stricture alone.

4. *Other types of focal malacia of the trachea and main stem bronchi* may occur and produce expiratory airflow obstruction of a type clinically indistinguishable from conventional obstructive pulmonary emphysema. Figure 11, *A* and *B* shows the relevant lesions in a 32 year old laborer who was unable to exhale forcibly or to clear secretions, especially from the right base. He dated the onset of respiratory impairment to a severe purulent tracheobronchitis 2 years previously. Conventional inspiratory bronchograms are normal. Expiration and especially coughing produce subtotal occlusion of the distal trachea by exaggerated invagination of its left posterolateral wall. A mild laxity of this very segment is often seen, both during bronchography and bronchoscopy, and has been attributed to the entrance of blood vessels and nerves supplying the distal trachea. A similar flaccid area is present in the posteromedial wall of the bronchus intermedius, which caused total occlusion evident at the beginning of the examination. Contrast medium only passed beyond this area after the bronchographic catheter was inserted directly through it. However complete the

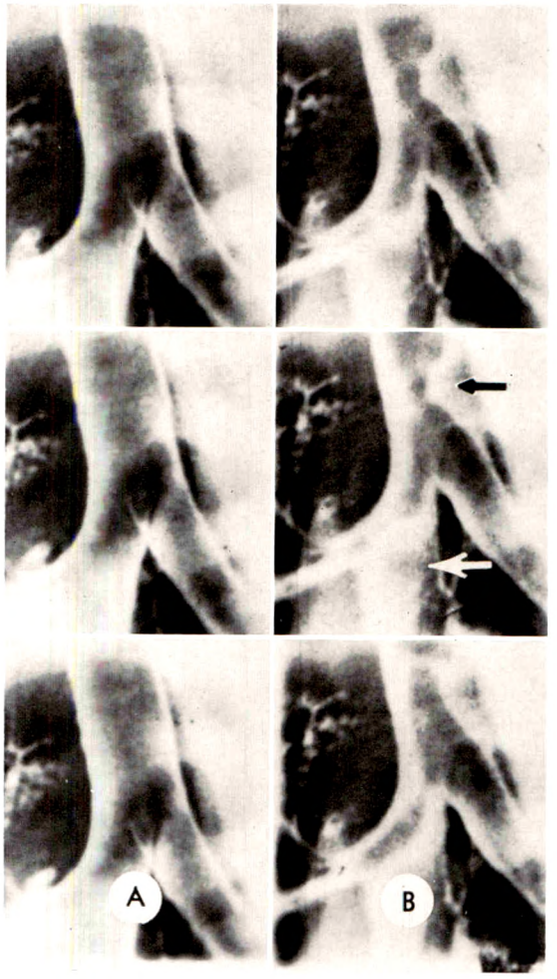


Fig. 11. Postnecrotic malacic areas of major airways. (*A*) Inspiration. Normal morphology. (*B*) Expiration. Striking stenosing invaginations of membranous part of distal trachea (black arrow) and of bronchus intermedius (white arrow). The combined effect of both lesions causes total obstruction of flow of air and secretions to and from the right middle and lower lobes which are totally bronchiectatic and functionally inert. The tracheal stenosis alone affects the right upper lobe and the entire left lung by impeding expiratory airflow (obstructive emphysema).

degree of stenosis, the lesion is soft and apparently consists of a malacic portion of bronchial wall, as proved by the fact that the soft bronchographic rubber catheter could easily be slipped through it during inspiration. Even after removal of the catheter, however, no air or secretions pass across this flap at any time. This dual obstructive mechanism has resulted in advanced sac-

cular and cylindrical bronchiectasis of the right middle and lower lobes which have become functionally inert. The remainder of the respiratory parenchyma (right upper lobe and the entire left lung) is only affected by the tracheal expiratory stenosis, and consequently shows air trapping characteristic of obstructive emphysema but without the cinebronchographic findings noted in the case of diffuse stenosis at the level of the terminal bronchioles (see Figure 6, *A* and *B* above). Figure 11*B*, incidentally, illustrates well the airflow pattern during expiration, in particular that the entire air exchange on the right side takes place from the right upper lobe. Both the tracheal and bronchial lesions were confirmed by bronchoscopy soon after cinebronchography. It appears plausible to consider that the purulent tracheobronchitis which marked the onset of this patient's respiratory disability is the etiologic factor, probably through the mechanism of focal tissue destruction or chronic ulcerations with incomplete healing. It is of interest that a partial curative procedure was attempted by strutting of the distal trachea according to the method described by Rainer *et al.*[9] and Herzog.[7] Marked but only partial improvement occurred. The improvement involved specifically the emphysema component of the disease. The intermediate bronchus was not treated, and that portion of the patient's symptoms related to the bronchiectasis, the inability to clear secretions or ventilate the right middle and lower lobes, persisted.

DISCUSSION

I. THE ROLE OF CINEFLUOROGRAPHY IN BRONCHOGRAPHY

Bronchography is one of the branches of diagnostic radiology best complemented with cinefluorography because satisfactory roentgen contrast is easily achieved, and because a number of rapidly occurring, diagnostically significant events require understanding and interpretation. There are four broad reasons why cinefluorography especially enhances the value of bronchography, over and above the merits of fluoroscopy *per se*:

1. The accurate recording of tracheobronchial dynamics for correlation with physiologic data and clarification of morphologic-functional relationships.

2. The visual appraisal of pulmonary compliance and of the excursions of chest wall and diaphragm.

3. The distinction of transient from permanent defects, be they intratracheal, intrabronchial, mural, or peribronchial.

4. The facilitation of spatial orientation of lesions, and directional orientation of dynamic events.

II. SPECIFIC CONTRIBUTIONS OF CINEFLUOROGRAPHY TO THE CLINICAL EVALUATION OF VENTILATORY DYSFUNCTIONS

The study of cinebronchograms has yielded a high degree of diagnostic accuracy, even in early and clinically as yet ill-defined cases. Conversely, without cinefluorography, the over-all value of bronchography is severely limited. The specific contributions of cinefluorography in cases with ventilatory defects can be summarized under two major headings:

1. The effectiveness of ventilation can be estimated visually by gauging air exchange and parameters of pulmonary compliance such as mobility of the peripheral bronchi, and by noting the ease of peripheral filling in relation to air trapping. These features provide a measure of the functional capacity of units of the lungs (with an accuracy which at times is comparable to bronchospirometry), and in comparing the relative functional competence of certain units, such as lobes, with respect to others.

2. Several distinct types of tracheobronchial deformities are recognized in relation to airflow impedance (Fig. 12). These deformities must be analyzed and classified in terms of their dynamic behavior in order to understand their effect on respiratory function. Peripheral to the hilar areas, at any given time the configuration of a bronchus is determined by the interaction between: (a) the mechanical characteristics

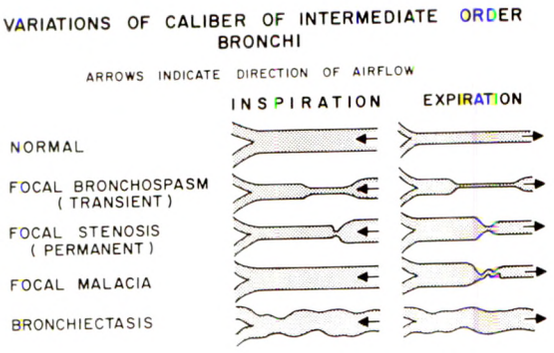


FIG. 12. Typical bronchial deformities.

of the bronchial wall (elasticity, resistance, shape in cross section and longitudinally), (b) traction exerted by the elastic pulmonary parenchyma, and (c) the opposing transmural action of intrathoracic and intraluminal pressures. The intraluminal pressure in turn is conditioned by the volume of displaced air, the velocity of flow of the air mass, and of the mechanical airway resistance encountered, modified by factors such as bronchial mucosal surface tension and aerodynamic flow laminations. In the trachea and main stem bronchi, the relationships between physical dimensions and intraluminal air flow and pressure are based on similar considerations, except that the large airways are not in contact with lung. Therefore, they are not subject to its elastic force but continue to be affected by intrathoracic pressures up to the thoracic inlet. Intrathoracic pressure of course is not operative in the cervical portion of the trachea. In the future, simultaneous recording of data including intraluminal pressure and flow determinations will shed more precise light on these phenomena.

III. THE PHENOMENON OF FOCAL TRACHEO- OR BRONCHOMALACIA

Repeated observations of focal buckling of intermediate size bronchi in cases with obstructive defects of respiration suggest that this is a fundamental mechanical pathologic entity which apparently occurs with great frequency but with varying degrees of intensity, predominantly in cases of well established chronic bronchitis. Occasionally, other etiologic conditions have been identified as illustrated in several cases above. It cannot be emphasized too strongly that bronchomalacia will remain undetected on conventional studies because the lesion, by its very nature, only occurs as an integral part of active expiration or coughing. When expiratory flow stops, and throughout inspiration, this lesion effaces itself readily and only the organic changes produced by it peripherally are recognized and are, then, often considered primary. In fact, however, a soft segment of bronchus can be seen to buckle immediately as soon as expiration or cough begin, so that the parenchyma peripheral to this lesion is prevented from evacuating its contents while remaining subject to the same diffuse intrathoracic pressure. It is thought that such a localized expiratory flow obstruction, with continuous repetition of respiratory cycles, may cause gradual disruption of the structural integrity of the bronchial walls distal to the stenosis, associated with trapping of secretions and possibly air. The morbid changes in such a system are apt to occur at the weakest point, which in some individuals may be at the level of the alveolar sacs, in others in the bronchioles, and in others in the smaller bronchi, especially if these are weakened by pre-existing chronic inflammatory infiltration. Evidently this mechanism can produce obstructive emphysema, or bronchiectasis, or a combination of the two. As ventilatory impairment associated with obstructive emphysema and/or bronchiectasis progresses, it is obvious that areas of lung can gradually become completely defunctionated.

The occurrence and significance of paradoxic variations of bronchial caliber in respiratory disease associated with increased expiratory airflow resistance have been discussed by Fraser,[3] Macklem *et al.*,[8] and Rainer *et al.*,[9] who have made quantitative determinations of bronchial dimensions at various levels during several phases of respiration, as well as correlation with endobronchial and extrabronchial pressure and

flow determinations. Their studies, however, pertain primarily to the large airways. The implication of this mechanism in the more general pattern of pulmonary obstructive diseases of various types is now becoming apparent. The importance of cough against outflow obstruction has also been indicated by Rayl[11] and Dekker and Ledeboer,[2] and the ease with which the membranous part of the trachea and main stem bronchi invaginates to produce expiratory flow obstruction has also been described by Herzog,[7] Rainer *et al.*,[9] and others, and is illustrated in one of our cases above.

Although one encounters diverse etiologies of bronchomalacia, the ultimate culprit in the majority of cases is obviously chronic bronchitis. The etiologic relationship of chronic bronchitis to pulmonary emphysema and bronchiectasis is suspected in many parts of the world, especially in Great Britain.[1,5]

SUMMARY

The unique contributions of cinefluorography to bronchography in elucidating important physiologic processes are illustrated and discussed within the framework of a practical simple classification of ventilatory dysfunctions of respiration. Cinefluorography has been found especially dependable in the assessment of local, regional or general ventilatory adequacy, and in the recognition, appraisal, and interpretation of several typical tracheobronchial deformities, most of which remain unrecognized or undifferentiable by conventional studies.

Among these lesions, attention is called specifically to the phenomenon of tracheo- or bronchomalacia, or expiratory buckling of diseased portions of trachea or bronchi. This entity, most often the result of chronic bronchitis although other types occur, appears to be crucial in the pathogenesis of many cases of obstructive emphysema and bronchiectasis. It can only be observed *in vivo* during active expiration or cough.

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Vol. 99, No. 3

A COMPARISON STUDY OF LARYNGOGRAPHY TECHNIQUES*

150 KVP. PLAIN ROENTGENOGRAPHY *vs.* POSITIVE CONTRAST ROENTGENOGRAPHY

By JOHN R. THORNBURY *and* HOWARD B. LATOURETTE
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IN 1965, Maguire and his colleagues[1] described the use of selective filtration of the diagnostic roentgen-ray beam to obtain high kilovoltage roentgenograms of the larynx. The use of 140 kvp. quality roentgen-rays with 1 mm. added brass filtration (more recently Maguire[2] used 130 kvp. with 1 mm. brass filtration) produces roentgenograms of the larynx having an appearance similar to that noted on tomograms. The air column is prominently demonstrated and the underlying bony structures are partially deleted.

This technique has the advantage of short exposure times as compared to tomography. Therefore, the standard laryngography maneuvers (respiration, phonation, full and modified Valsalva maneuver, and reverse phonation) can be performed using the high kvp. brass filtered technique. This method also has the advantage of not requiring preliminary medication and topical anesthesia, as is necessary for positive contrast laryngography.

Our preliminary evaluation of the high kvp. technique suggested that better airway delineation and deletion of the underlying bony structures could be achieved by using 150 kvp. and 3 mm. of brass filtration.

During the period of January to April 1966, a comparison study of 150 kvp. (3 mm. brass filter) plain roentgenography with positive contrast laryngography was performed in a consecutive series of 15 patients at the University of Iowa Hospitals. All patients had biopsy-proven laryngeal tumors and were evaluated in conjunction with the Department of Otolaryngology.

The two techniques were performed on each patient on the same day, with the 150 kvp. examination preceding the positive contrast examination. At the end of the comparison study, the roentgenograms of all cases were reviewed. Comparison of the visualization of the extent of the tumor and the subglottic region was made. Admittedly, there is considerable subjective impression involved in such a comparison.

TABLE I

DISTRIBUTION OF LARYNGEAL TUMORS

Tumor Site	No. of Cases	Subglottic Extension
Glottic	6	1
Supraglottic	6	0
Transglottic	3	3
Total	15	4/15

TABLE II

COMPARISON OF TUMOR DETECTION

	Glottic	Supraglottic	Transglottic	Subglottic Extension
Seen on positive contrast roentgenogram	6	6	3	4
Seen on 150 kvp. roentgenogram	4	6	3	4

* Presented at the Fourteenth Annual Meeting of the Association of University Radiologists, Little Rock, Arkansas, May 12–14 1966.

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TABLE III

COMPARISON OF TUMOR DELINEATION

	Glottic	Supraglottic	Transglottic	Subglottic Extension
Seen better on positive contrast roentgenogram	5	3	1	1
Seen better on 150 kvp. roentgenogram	0	0	2	2
Seen equally well on both	1	3	0	1

However, an attempt was made to diminish this bias by first evaluating, as unknowns, the 150 kvp. roentgenograms in the 15 patients as a group for presence and extent of tumor and then similarly evaluating the positive contrast laryngograms. Subsequently, the two techniques in each case were compared in corresponding film pairs.

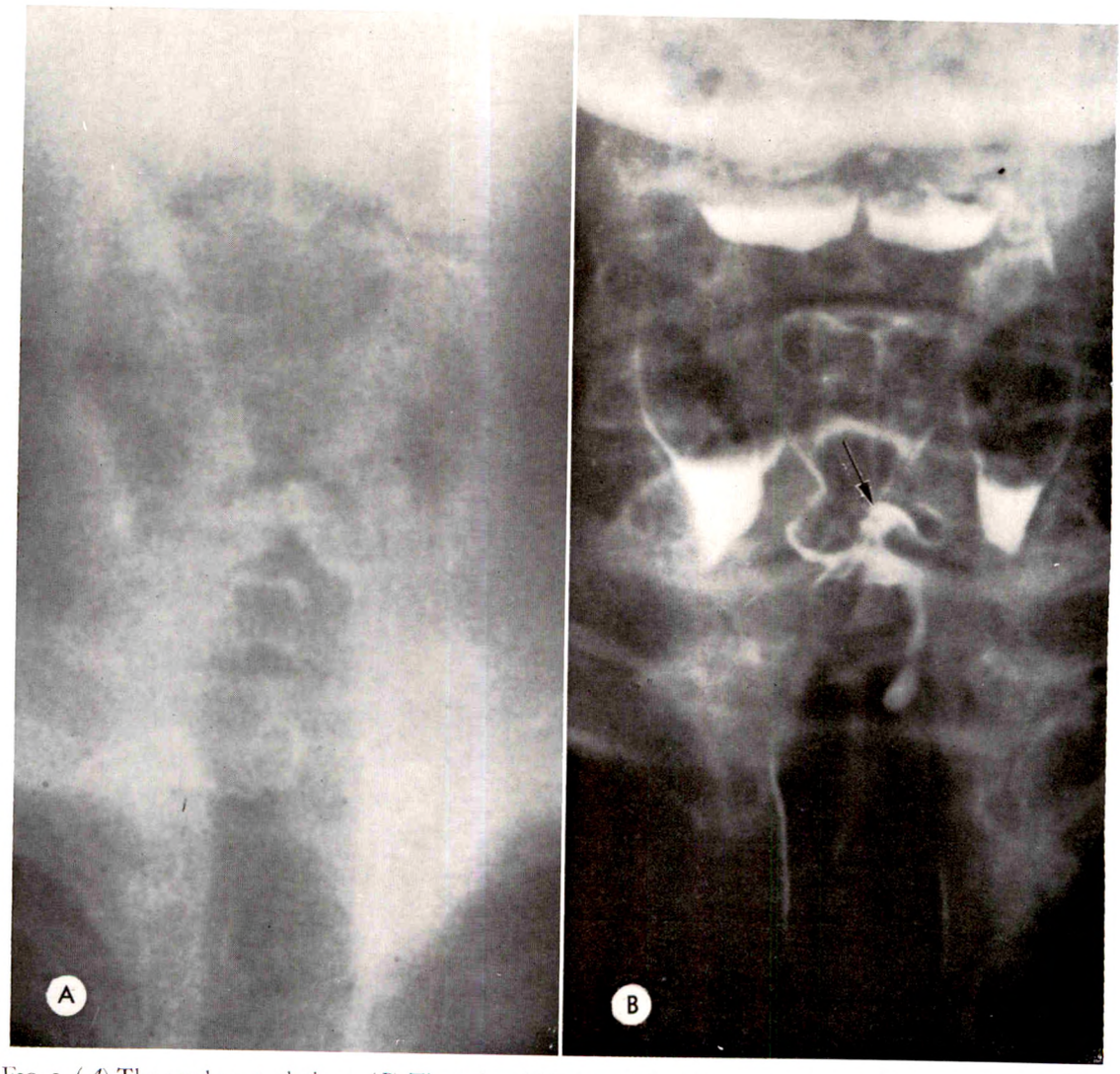


FIG. 1. (*A*) The 150 kvp. technique. (*B*) The polypoid lesion of the left true vocal cord is better delineated by the positive contrast technique (arrow).

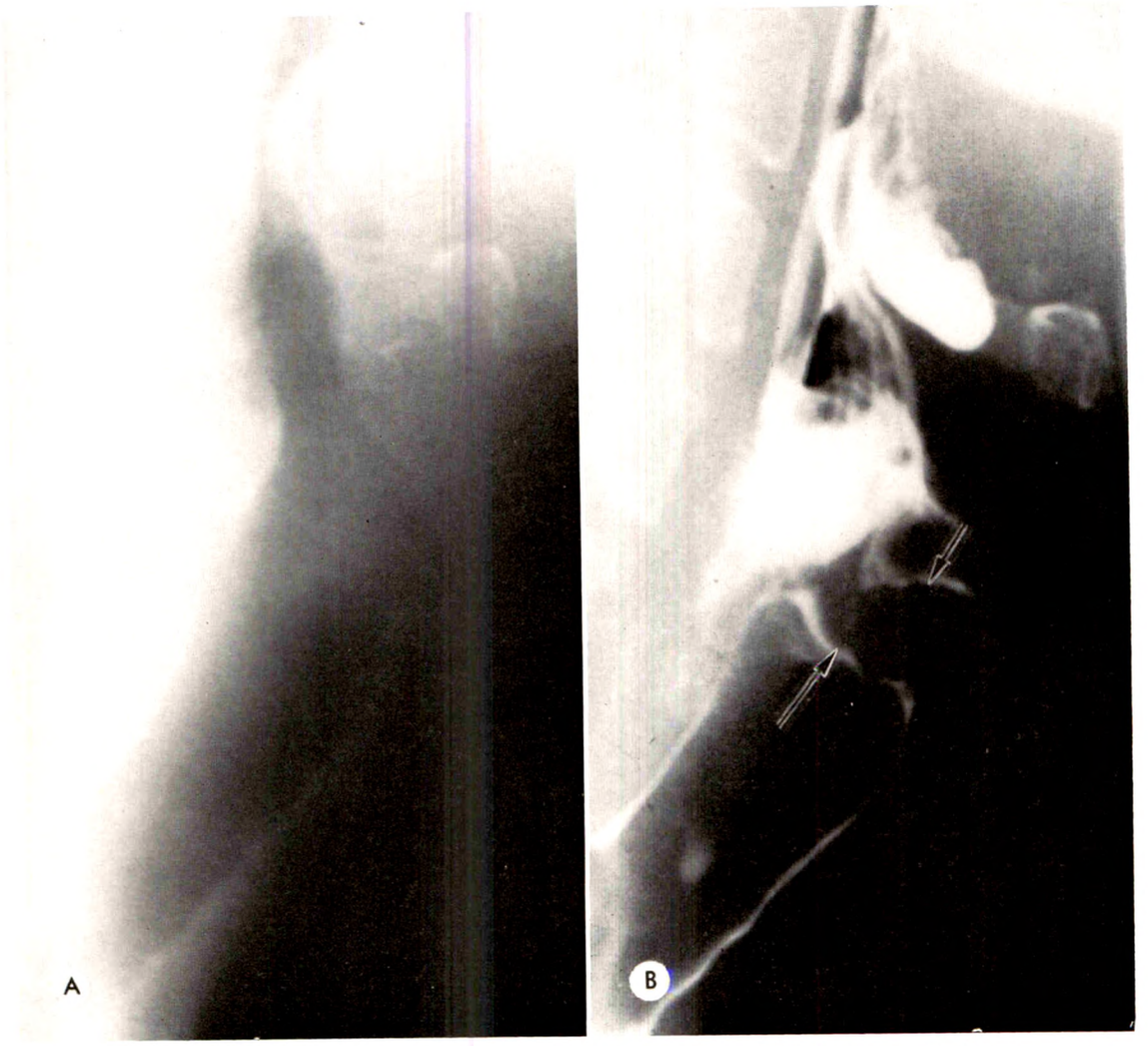


FIG. 2. (*A* and *B*) Lateral views of the tumor shown in Figure 1, *A* and *B*. The extent of the lesion (arrows in *B*) cannot be seen on the 150 kvp. roentgenogram (*A*).

TECHNIQUE

The 150 kvp. technique was performed in the following manner. The patient received instruction in the laryngographic maneuvers and practiced them until the radiologist was satisfied. Then he was seated in the anteroposterior position in front of a standard chest board, and each maneuver was recorded on a separate film and identified by a lead marker. A lateral roentgenogram of the larynx during quiet respiration was also made. Positive contrast laryngography was performed as described by Powers *et al.*[4] using oily dionosil.

The technical factors of the 150 kvp. roentgenography (using three-phase equipment) were as follows: (a) focal film distance, 40 inches; (b) 150 kvp.; (c) 3 mm. brass filtration; (d) 300 ma.; (e) 2 mm. focal spot; and (f) a phototimer (Iontomat). The Iontomat setting was usually −3 which, with our equipment, corresponds to 1/20–1/30 second exposure time. Parspeed screens and Du Pont Cronex II film were used. No grid was employed. The films were developed in an automatic processor.

RESULTS

The tumors encountered in the 15 patients are classified in Table 1. The term "transglottic" is used at the University of

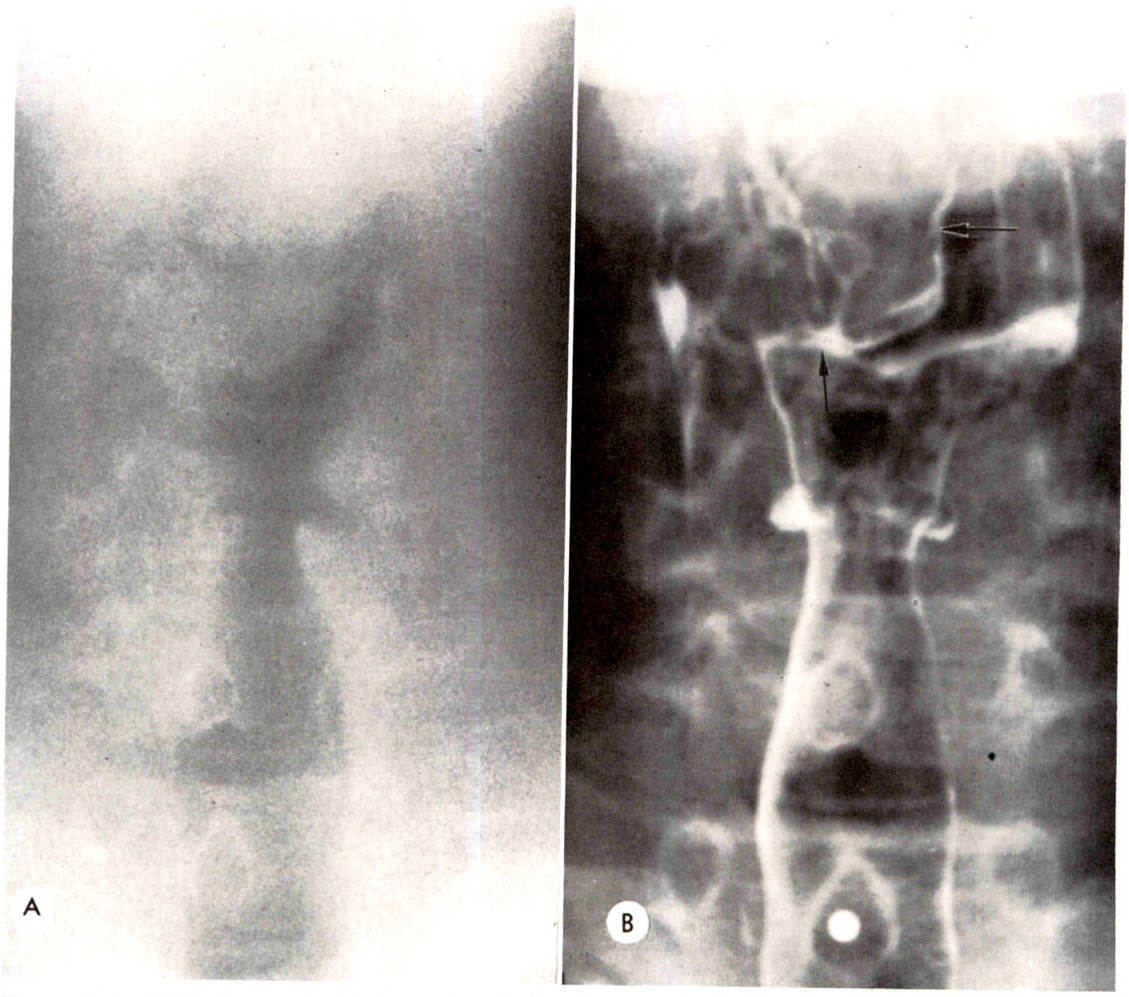


Fig. 3. (*A* and *B*) The extent of a large supraglottic tumor involving the epiglottis, valleculae, and right aryepiglottic fold is better shown on the positive contrast roentgenogram (arrows in *B*).

Iowa Hospitals to describe tumors which encompass the glottic and supraglottic regions. Detection and delineation of the tumors by the two techniques are compared in Table II and III.

In the glottic tumors, the detection of the tumor was superior using the positive contrast technique (Fig. 1, *A* and *B*; and 2, *A* and *B*). The two tumors not detected using the 150 kvp. technique were a small polyp of the left true cord and a diffuse right true cord lesion, which produced only a mild degree of thickening of the involved cord as seen on the positive contrast laryngogram.

Both techniques were of equal accuracy in tumor detection in the supraglottic and transglottic lesions. In regard to the extent of delineation of the tumor margins, the positive contrast technique was superior to the 150 kvp. technique in supraglottic lesions (Fig. 3, *A* and *B*; and 4, *A* and *B*), while the 150 kvp. technique was more satisfactory in the transglottic tumors (Fig. 5, *A* and *B*). The main reason for the inadequacy of positive contrast in the transglottic tumors was poor contrast coating of the inferior extent of these large bulky tumors. Patients with large transglottic tumors frequently experienced difficulty in performing the maneuvers while under the influence of premedication, topical anesthesia, and introduction of the contrast medium. This coupled with the airway embarrassment due, simply, to the tumor

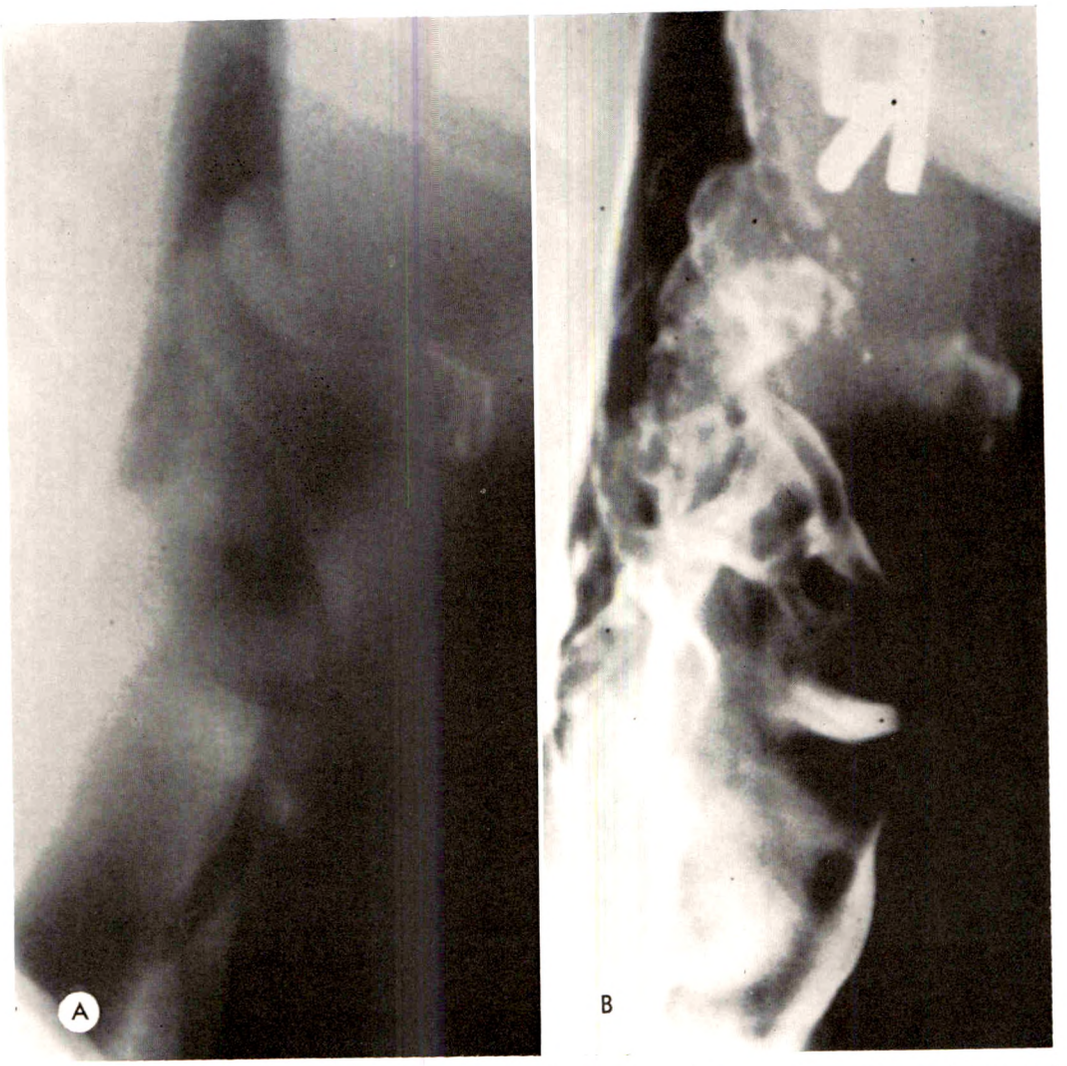


FIG. 4. (*A* and *B*) Lateral views of the same tumor as in Figure 3, *A* and *B*. The surface and extent of the tumor are much better shown by the positive contrast roentgenogram (*A*).

size and location (which was augmented by anesthesia and contrast medium instillation), often resulted in an apprehensive patient whose cooperation was quite restricted.

Subglottic region visualization is compared in Table IV. For the most part, this region was satisfactorily demonstrated by both techniques (Fig. 6, *A* and *B*). Visualization of involvement by tumor was slightly better with the 150 kvp. technique, but the number of cases is small. Subglottic involvement was frequent in this group of 15 patients with an incidence of 27 per cent.

COMMENT

In our comparison study, positive contrast laryngography was more accurate than the 150 kvp. technique in tumor detection and delineation. The only exceptions to this were the few transglottic lesions in which technically satisfactory positive contrast studies were difficult to obtain. The visualization of the subglottic region, using the 150 kvp. technique, was as accurate and efficacious as the positive contrast technique.

Therefore, it is our opinion that the procedure of choice for laryngography is positive contrast roentgenography. However,

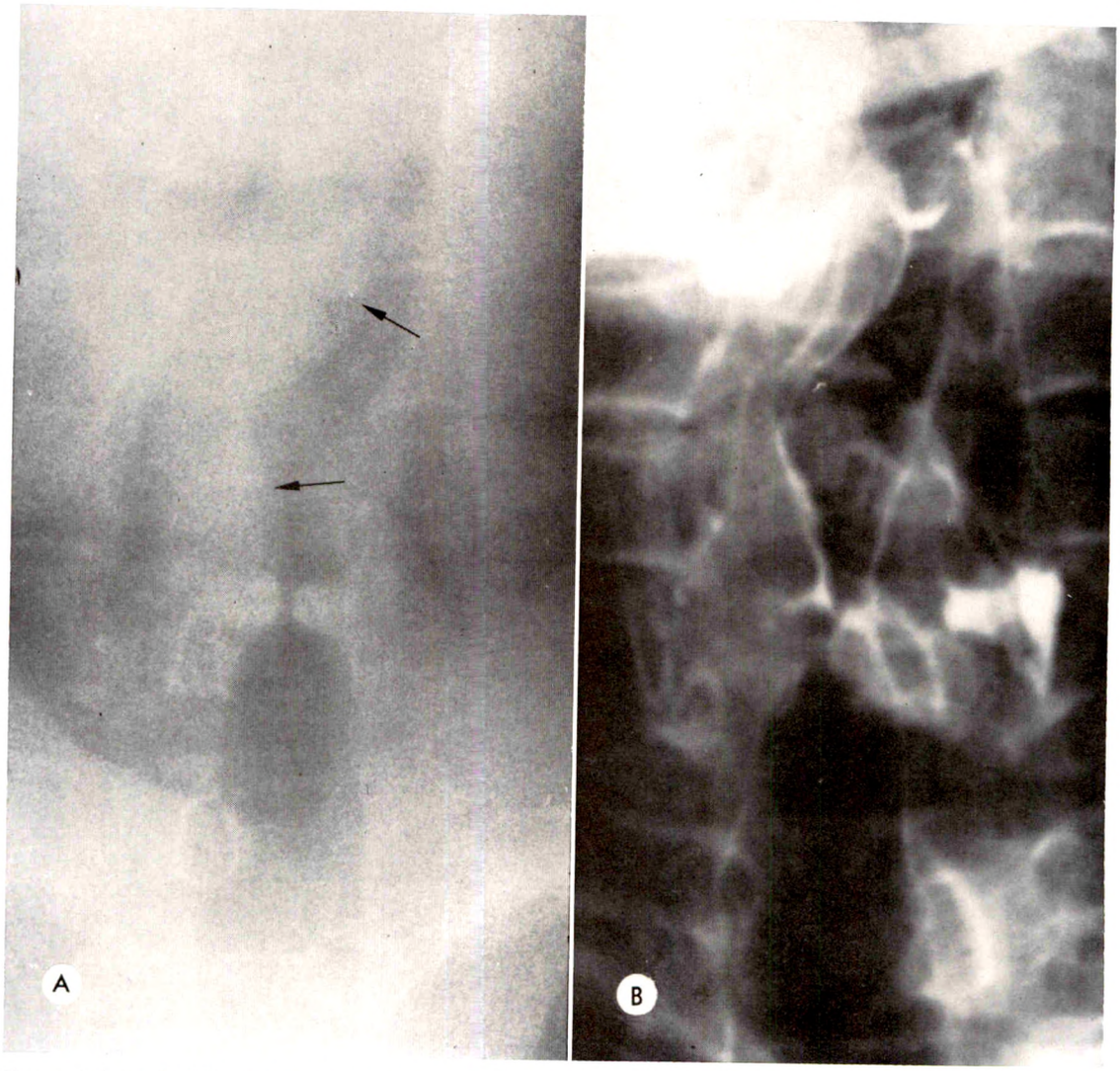


FIG. 5. (*A* and *B*) The extent of a large transglottic lesion on the right is poorly shown on the unsatisfactory positive contrast roentgenogram (*B*). The 150 kvp. roentgenogram shows well the uninvolved subglottic region.

150 kvp. plain roentgenography provides an alternative method in several situations: (1) when a positive contrast examination is inadequate due to technical problems (*i.e.*, unsatisfactory anesthesia and/or contrast coating); (2) when the tumor obstructs the airway to such an extent that the use of topical anesthesia and contrast medium instillation is contraindicated; and (3) when atropine premedication is contraindicated. If the radiologist subscribes to the view of Medina *et al.*[3] that the major practical contribution of laryngography is in the detection of subglottic involvement by tumor, then perhaps he would feel more inclined to use 150 kvp. plain roentgenography as the procedure of choice, since it is as accurate as the positive contrast technique in this regard.

SUMMARY

1. In a series of 15 patients having laryngeal tumors, positive contrast laryngography was found to be superior to the 150 kvp. plain roentgenography in both tumor detection and delineation.

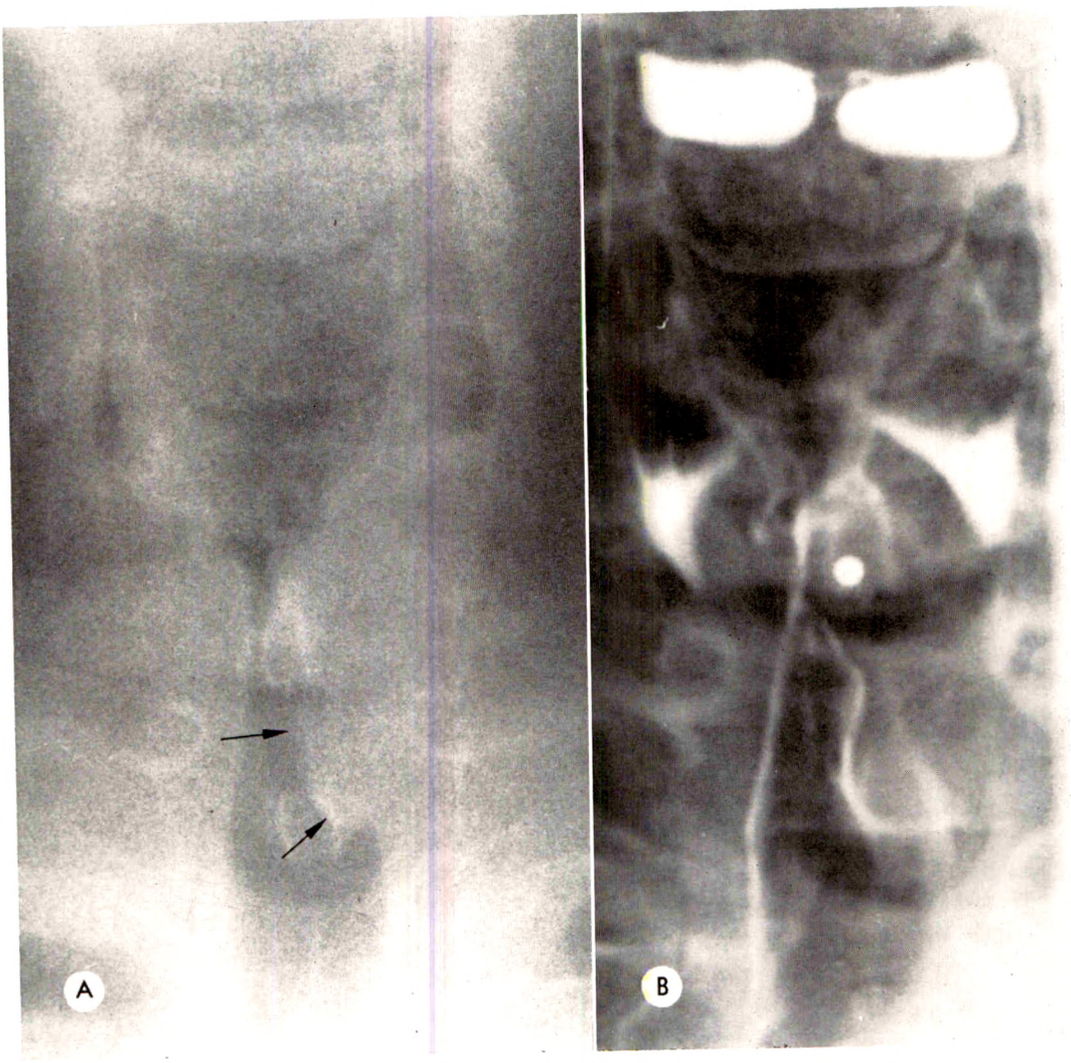


Fig. 6. (*A* and *B*) Subglottic extension of a large left true vocal cord tumor (arrows in *A*) is well shown by both techniques.

Table IV

Comparison of Subglottic Region Visualization: All Cases

Seen better on positive contrast roentgenogram	3
Seen better on 150 kvp. roentgenogram	3
Seen equally well on both	9

2. However, the subglottic region was equally well visualized by both techniques.

3. When positive contrast laryngography is technically unsatisfactory or contraindicated, 150 kvp. plain roentgenography offers an alternative method, especially as regards evaluation of subglottic involvement by tumor.

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NASAL PRESSURE CHANGES DURING SWALLOWING*

AN ANALYSIS OF 1,219 SWALLOWS IN 88 HEALTHY SUBJECTS

By RAYMOND GRAMIAK, M.D.,† MAURICE L. KELLEY, Jr., M.D.,‡ *and* RICHARD F. GRAVINA, B.S.§

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RADIOLOGY has played a major role in researches concerning the mechanics of deglutition. This has been accomplished by fluoroscopy and high-speed cineradiography.[1–3,7,8,10,11] These studies have provided an accurate, sequential, but purely qualitative description of events during the early stages of deglutition. A reliable, innocuous, and simple method, which permits measurement of the dynamics of swallowing, is also needed to provide additional information about this rapid and complex process.

Characteristic pressure deflections occur in the closed nasal cavity during swallowing and reflect specific physiologic events in the mouth and pharynx. This research was undertaken to describe qualitatively and quantitatively the nasal pressure changes during swallowing in a large number of healthy subjects and to determine the effect of size and consistency of the bolus and position of the subject on the nasal pressure tracing.

BACKGROUND

Toynbee (1853) is generally credited with the observation that swallowing during nasal occlusion produces a pressure fluctuation in the closed nasal cavity.[12] Perlman,[9] almost a century later, recorded these pressure changes and speculated about their cause. Gramiak and Kelley,[5] combining nasal manometry and cineradiography, identified the oropharyngeal forces responsible for these pressure phenomena and described and classified the various nasal pressure changes.

These changes, as recorded manometrically, may be classified into four basic types (Fig. 1) that have common characteristics as well as specific differences. Each begins with a rapid positive deflection reaching a maximum point early in the swallowing sequence. This is followed by a generally negative deflection with a discrete maximum negative point developing near the end of swallowing. Termination occurs with a typically abrupt positive complex of events. The differences are shown in the tracings of the four types. In Type I, the initial positive deflection (IPD) is followed by a smooth downward trend to a maximum negative point (MNP) terminating with an abrupt positive deflection (APD). In Type II, the initial positive peak is similar to that of Type I but the smooth downward decline of the pressure gradient is interrupted by the formation of a plateau in the mid portion. The Type III pressure curve resembles Type I except for a cleft initial peak. Type IV is a complex of events combining the features of Types II and III, and shows a double initial peak with a plateau in the mid portion of the decline of the pressure gradient.

Simultaneous cineradiographic studies revealed that the initial positive deflection requires velopharyngeal closure and is the result of delivery of the bolus against the soft palate. The maximum initial positive deflection (MIPD) corresponds to entry of

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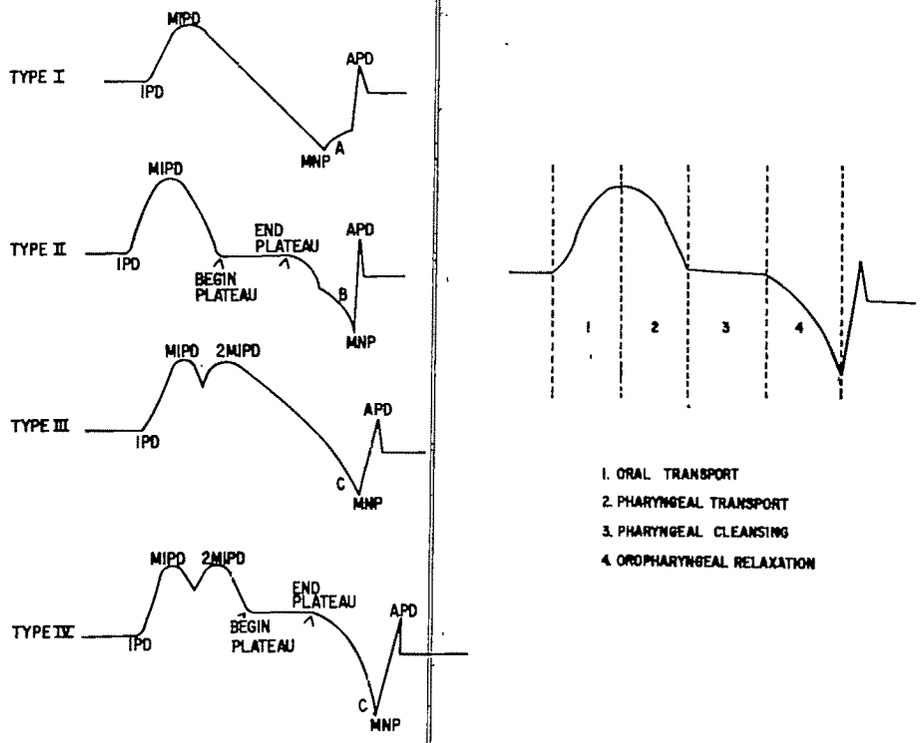


Fig. 1. Schematic representation of the four types of nasal pressure curves recorded during deglutition. IPD = initial positive deflection; MIPD = maximum initial positive deflection; 2MIPD = second maximum initial positive deflection; MNP = maximum negative pressure; APD = abrupt positive deflection. A, B, and C identify terminal complex varieties related to glottic opening and re-entry of air into the pharynx.

On the right a Type II nasal pressure curve has been subdivided into 4 phases reflecting oropharyngeal function with deglutition.

the bolus into the pharynx. Decline of the pressure gradient at this point is the consequence of opening of the cricopharyngeus and emptying of the pharynx under the influence of the tongue and pharyngeal constrictors. The second maximum initial positive deflection (2MIPD) seen in the Type III and Type IV tracings is the result of contact of the tongue against the soft palate in the course of its rolling contraction, and by means of which the tail of the bolus is delivered into the pharynx. The plateau seen in the Type II and Type IV pressure curves is due to the sustained contraction of the opposed tongue and pharyngeal constrictors. It corresponds to the time of emptying of the hypopharynx, after the bolus has traversed the upper pharynx. Termination of the plateau is characterized by resumption of negative deflection of the pressure gradient and is associated with relaxation of the propulsive elements of swallowing. The maximum negative pressure is the culmination of the downward movement of the pharynx. The abrupt positive deflection signalling the end of swallowing results from palatopharyngeal separation. Entry of air through the glottis occurs when the negative pressure is near its maximum and can be correlated with added pressure deflections in some instances. When glottic opening occurs well before the maximum negative pressure is achieved it may be associated with a positive pressure gradient superimposed on the generally negative trend and is designated as Variety B. When glottic opening occurs later, a positive wave may be produced between the point of maximum negative pressure and the onset

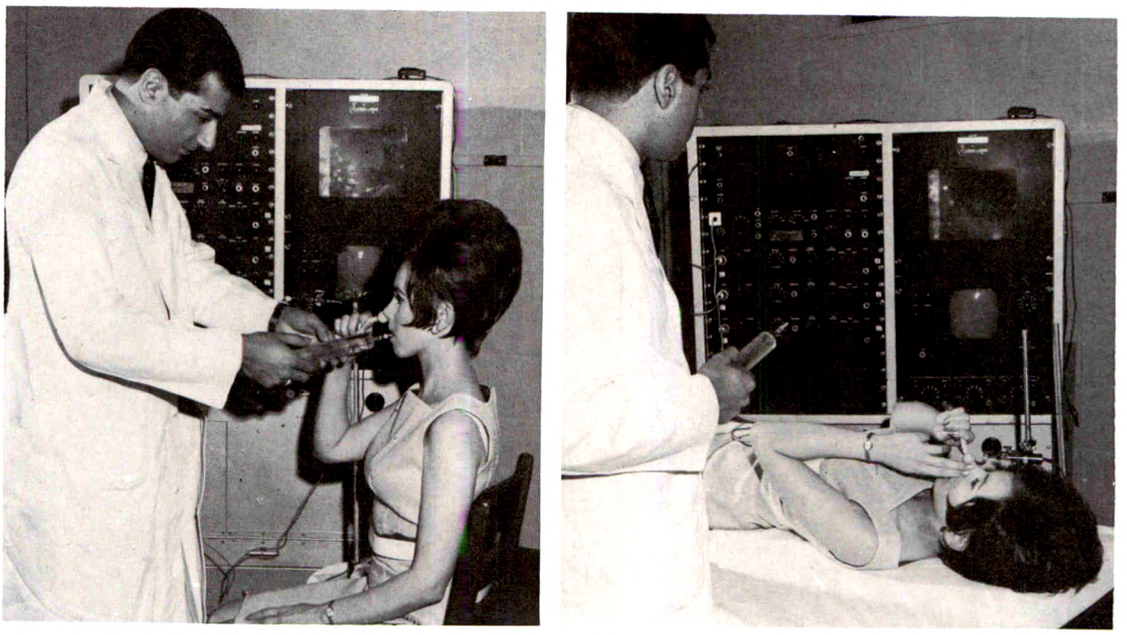


FIG. 2. Technique for recording nasal pressures during swallowing. Study with subject upright (left) demonstrates use of syringe for accurate bolus delivery. The subject has inserted the occluding nasal catheter. With subject supine (right) note use of two finger occlusion of the other nostril.

of the abrupt positive deflection. This is called Variety A. Terminations without deflections due to the entry of air are designated Variety C.

To summarize the functional events related to the nasal pressure curve, the interval between the onset of the initial positive deflection and its maximum point represents oral delivery of the bolus to the pharynx. Pharyngeal transport takes place between the peak of the initial positive deflection and the beginning of the plateau. The duration of the plateau represents the cleansing phase during which adherent residues are squeezed out of the pharynx. The interval between the end of the plateau and the maximum negative pressure reflects relaxation of the propulsive elements (Fig. 1).

METHOD

Eighty-eight healthy subjects were studied; 42 were men and 46 were women. The range in age was 18 to 51 years; the mean, 26 years. For each examination, the subject swallowed a series of boluses first in the upright and then in the supine position. With each position, the following series of swallows was performed: water 30 cc.; watery barium suspension, 30 cc.; watery barium suspension, 10 cc.; thick barium paste,* a spoonful. The liquids were administered by syringe to assure accuracy (Fig. 2). The quantity of barium paste administered by spoon was more difficult to determine. The average volume was 6.2 cc.; average weight, 14 gm. Each subject swallowed a minimum of 8 times. However, many performed additional swallows because of failure to manage a particular bolus successfully or because of enthusiasm when successes were easy to achieve.

A plastic, disposable, barium enema tip with side holes covered served as an occluding nasal catheter. It was 12 cm. long, had a uniform internal diameter of 0.6 cm., and was connected to a semirigid plastic tube that was 36 cm. long and had an internal diameter of 0.47 cm. The catheter in turn connected to a Statham pressure transducer, P23-Db. The entire system was water-filled with 10 ml. of water. The trans-

* Microtrast, produced by Damancy & Co., Ltd., Ware Herts, England.

ducer was placed at the approximate level of the subject's soft palate. A pulse wave detector was placed on the chest and secured with a belt to record chest movements. Prior to swallowing, the subject covered the open nostril with two fingers and maintained closure until the swallowing act was completed (Fig. 2).

Pressure recordings were made photokymographically on an Electronics for Medicine multichannel recorder, model DR-8, at a paper speed of 100 mm./sec.

The sensitivity of the recording apparatus was calibrated so that a pressure deflection of 16.2 mm. represented 10 mm. of Hg pressure. All records were reviewed by two of us (RG and MLK) to identify the nasal pressure events and to determine the type classification according to the previously defined criteria. For each pressure event, the time of occurrence in seconds after the initial positive deflection and the pressure in millimeters of mercury relative to resting nasal pressure were recorded. The information obtained was transferred to punch cards for recall and statistical analysis. After grouping by type and further subdivision as to subject position, bolus material, and bolus volume, the mean manometric and temporal characteristics of each pressure event were determined and the standard error calculated. Student's t test[4] was utilized to ascertain the significance of apparent differences and similarities in the magnitude of the pressure values and time of occurrence of the events on the nasal pressure tracings.

TABLE I

NASAL PRESSURE CHANGES WITH SWALLOWING

Distribution of Types			Frequency of Terminal Varieties in Per Cent		
	Number	Percentage	A	B	C
Type I	195	20.7	35.9	6.7	57.4
Type II	504	53.6	24.2	11.7	64.1
Type III	93	9.9	37.6	8.6	53.8
Type IV	148	15.8	29.0	9.5	61.5
All types	940	100.0	28.7	10.0	61.3

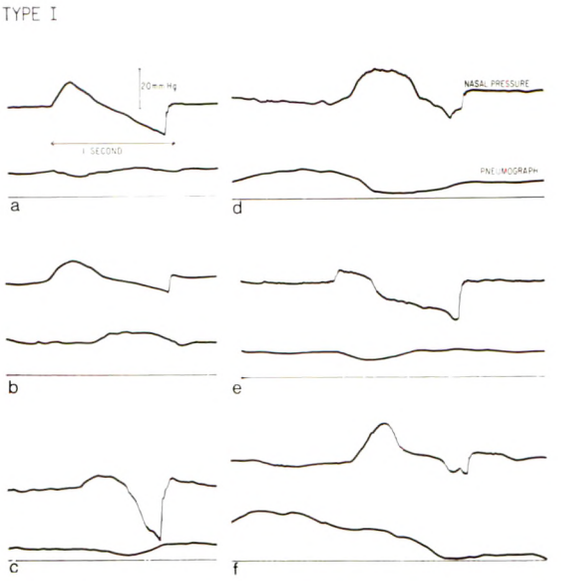


FIG. 3. Representative Type I nasal pressure curves with variability in the slope of the downward component are shown. Terminal complex varieties related to re-entry of air through the glottis are seen in c and f (Variety B), whereas Variety A is illustrated in d. The remaining tracings represent Variety C.

RESULTS

The total number of swallows recorded was 1,219 of which 940 were suitable for analysis. Repetitive swallows were discarded since determining the quantity of the physiologic response relative to volume depends on being reasonably certain about the amount of bolus transported. Other failures were designated as technically unsatisfactory because of inadequate or excessive activity of the nasal pressure tracings. Incomplete nostril occlusion produced inadequate pressure and hand, head or tongue movements unrelated to coordinated swallowing resulted in hyperactive tracings.

The frequency distribution of the four basic types encountered is shown in Table I and representative tracings are depicted in Figures 3 through 6. Individual subjects

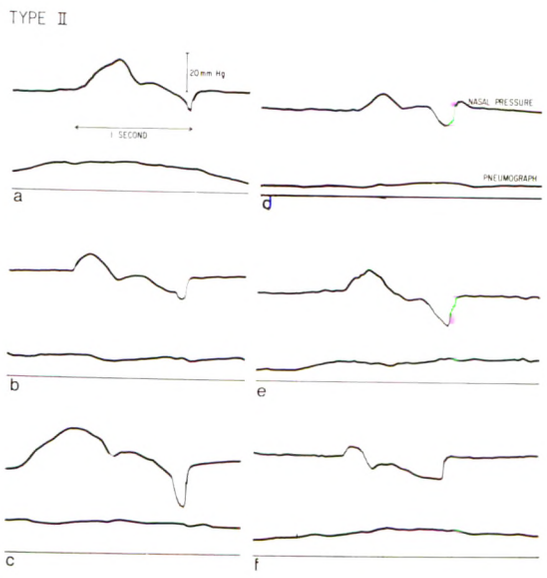


FIG. 4. Type II nasal pressure curves recorded during swallowing illustrate the variable onset pressure of the plateau. In a and c the plateau begins above resting nasal pressure, the others begin at or below resting.

demonstrated considerable variation in their swallowing patterns. Only 7 were restricted to one major type, all of whom produced Type II curves. Thirty-three subjects combined two types of swallowing patterns, 35 produced three types, and 13 demonstrated all four types.

There was no correlation between the type of curve produced and the size and consistency of the bolus or subject's position. The only departure from this general pattern occurred when the subjects were supine and had swallowed barium paste. Here the Type II nasal pressures fell from 53.6 per cent, the percentage for the whole group, to 39 per cent and the Type IV pressure changes increased from an over-all percentage of 15.8 per cent to 26 per cent. In all other instances, type distribution was the same for each bolus volume, bolus consistency or subject position as in the entire group.

Tables II through V summarize the major manometric and temporal data calculated from the nasal pressure curves; the data are classified according to type of nasal pressure change, position of subject, consistency of bolus, and size of bolus. In general, the maximum initial positive deflection was highest with the 30 cc. bolus; it was somewhat smaller with 10 cc., and

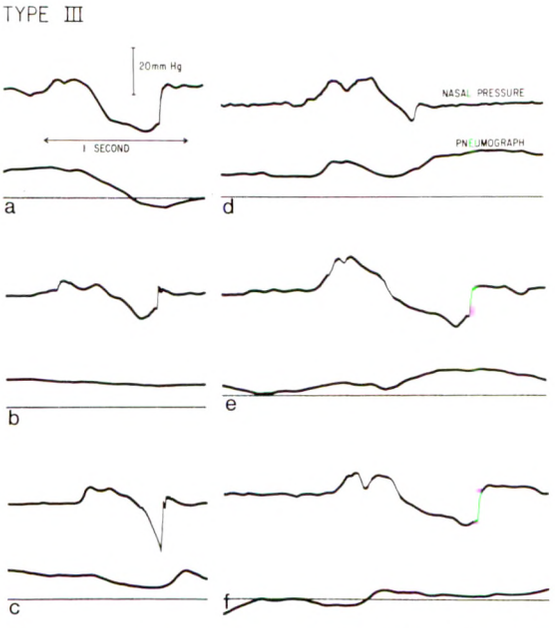


FIG. 5. Each tracing depicts the cleft initial peak characteristic of Type III nasal pressure curves. The downward gradient is continuous but shows the same variability present in Type I.

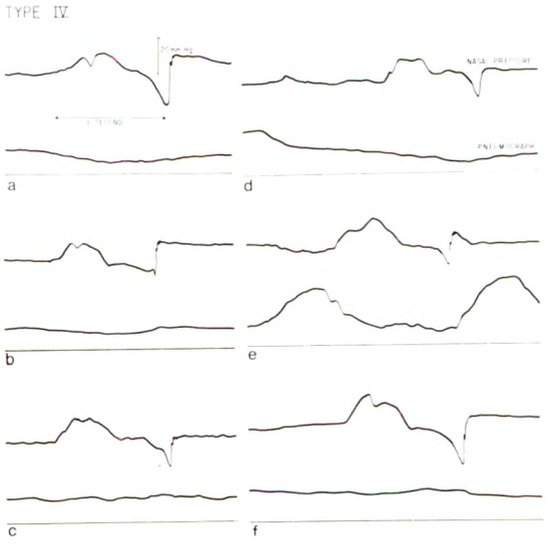


FIG. 6. Type IV nasal pressure curves, each with a double initial peak and a plateau. The plateau in a is short and shows a brief reversal of the negative pressure gradient.

TABLE II

TEMPORAL* AND MANOMETRIC† CHARACTERISTICS OF NASAL PRESSURE CURVES WITH SWALLOWING

Type I

	Upright				Supine			
Bolus material	Water	Watery barium	Watery barium	Barium paste	Water	Watery barium	Watery barium	Barium paste
Volume	30 cc.	30 cc.	10 cc.	spoonful‡	30 cc.	30 cc.	10 cc.	spoonful‡
Swallows	32	28	40	16	18	16	27	18
MIPD time	.22 (.03)	.20 (.03)	.17 (.03)	.17 (.02)	.26 (.03)	.30 (.04)	.20 (.03)	.16 (.02)
MIPD pressure	12.56 (1.30)	10.46 (1.12)	9.80 (1.07)	7.31 (1.05)	9.94 (1.15)	9.25 (1.11)	8.19 (.80)	7.67 (1.17)
MNP time	.84 (.03)	.81 (.03)	.73 (.03)	.74 (.04)	.89 (.05)	.96 (.06)	.85 (.04)	.78 (.04)
MNP pressure	10.69 (1.13)	11.71 (1.14)	9.83 (.66)	12.50 (1.77)	12.11 (1.65)	14.63 (1.33)	10.59 (1.01)	11.89 (1.17)
Beginning APD time	.89 (.03)	.85 (.03)	.78 (.03)	.84 (.04)	.93 (.05)	1.07 (.10)	.91 (.04)	.85 (.05)
Beginning APD pressure	−9.81 (1.21)	−10.93 (1.19)	−8.93 (.77)	−10.25 (2.04)	−10.94 (1.75)	−13.75 (1.24)	−9.41 (1.04)	−10.06 (1.34)
Maximum APD time	.92 (.03)	.90 (.04)	.82 (.03)	.87 (.04)	.97 (.05)	1.11 (.10)	.95 (.04)	.89 (.05)
Maximum APD pressure	1.41 (.58)	1.14 (.41)	1.63 (.57)	1.19 (.84)	2.78 (.97)	2.63 (.68)	1.26 (.47)	1.83 (.47)

* Expressed in seconds following the initial positive deflection.
† Figures represent millimeters of mercury above or below resting nasal pressure.
‡ Average volume 6.2 cc.
All figures are means. Those in parenthesis are the standard error of the mean.

lowest with barium paste. The amplitude varied from 1 to 32 mm. Hg. The pressure at the onset of the plateau was from −15 mm. Hg to +19 mm. Hg, although the means were usually only slightly below or above resting nasal pressure. Maximum negative pressure ranged from zero to −34 mm. Hg.

Time relationships also showed considerable variation. The time of maximum initial positive deflection ranged from 0.03 to 0.93 seconds. Similarly the time of onset of the plateau was from 0.11 to 1.23 seconds; of maximum negative pressure 0.37 to 1.98 seconds; and of maximum abrupt positive deflection 0.52 to 2.39 seconds. In most instances the mean total duration of the swallowing complex was about 1 second.

Analysis of the data presented in Tables II to V permits the following generalizations: (1) variations in the characteristics of the bolus produced variations in the pressure and timing of the nasal pressure curve; (2) similar bolus characteristics evoked similar manometric and temporal responses; (3) larger bolus volumes were associated with a higher maximum initial pressure deflection and produced a longer

TABLE III

TEMPORAL* AND MANOMETRIC† CHARACTERISTICS OF NASAL PRESSURE CURVES WITH SWALLOWING

Type II

	Upright				Supine			
Bolus material	Water	Watery barium	Watery barium	Barium paste	Water	Watery barium	Watery barium	Barium paste
Volume	30 cc.	30 cc.	10 cc.	spoonful‡	30 cc.	30 cc.	10 cc.	spoonful‡
Swallows	82	72	73	39	63	55	90	30
MIPD time	.18 (.01)	.18 (.01)	.13 (.01)	.18 (.03)	.19 (.01)	.22 (.02)	.17 (.01)	.18 (.02)
MIPD pressure	10.66 (.81)	9.25 (.82)	8.05 (.49)	6.69 (.69)	12.17 (.75)	11.89 (.74)	9.33 (.56)	6.73 (.87)
Beginning plateau time	.44 (.02)	.45 (.02)	.38 (.02)	.43 (.04)	.46 (.02)	.50 (.03)	.40 (.02)	.39 (.02)
Beginning plateau pressure	−.13 (.73)	−1.38 (.68)	−2.27 (.58)	−1.59 (.75)	2.38 (.62)	1.44 (.72)	.32 (.53)	−1.60 (.80)
Maximum plateau time	.58 (.03)	.58 (.02)	.51 (.02)	.56 (.05)	.60 (.02)	.63 (.03)	.53 (.02)	.53 (.03)
Maximum plateau pressure	2.44 (.69)	1.01 (.66)	−.34 (.59)	.51 (.77)	4.97 (.67)	3.42 (.75)	2.16 (.51)	1.77 (.90)
End plateau time	.68 (.03)	.69 (.02)	.59 (.02)	.69 (.05)	.75 (.03)	.77 (.03)	.67 (.02)	.73 (.04)
End plateau pressure	.76 (.70)	−.79 (.65)	−1.92 (.55)	−1.21 (.76)	3.19 (.68)	1.73 (.76)	.53 (.51)	−.50 (.88)
MNP time	.89 (.03)	.90 (.02)	.79 (.02)	.90 (.06)	1.00 (.03)	1.00 (.04)	.90 (.02)	.95 (.03)
MNP pressure	10.21 (64)	10.88 (.61)	11.36 (.67)	11.62 (.94)	11.02 (.75)	9.87 (.69)	10.86 (.64)	13.23 (1.20)
Beginning APD time	.94 (.03)	.96 (.02)	.84 (.02)	.94 (.06)	1.04 (.03)	1.03 (.03)	.94 (.02)	1.03 (.05)
Beginning APD pressure	−9.50 (.68)	−10.00 (.66)	−10.23 (.77)	−10.82 (1.04)	−10.44 (.78)	−9.24 (.73)	−10.00 (.67)	−12.47 (1.28)
Maximum APD time	.97 (.03)	.99 (.02)	.88 (.02)	.98 (.06)	1.08 (.03)	1.07 (.03)	.98 (.02)	1.07 (.05)
Maximum APD pressure	1.71 (.42)	.67 (.44)	.55 (.33)	2.28 (.61)	1.79 (.43)	1.55 (.39)	1.62 (.34)	2.27 (.82)

* Expressed in seconds following the initial positive deflection.
† Figures represent millimeters of mercury above or below resting nasal pressure.
‡ Average volume 6.2 cc.
All figures are means. Those in parenthesis are the standard error of the mean.

TABLE IV

TEMPORAL* AND MANOMETRIC† CHARACTERISTICS OF NASAL PRESSURE CURVES WITH SWALLOWING

Type III

	Upright				Supine			
Bolus material	Water	Watery barium	Watery barium	Barium paste	Water	Watery barium	Watery barium	Barium paste
Volume	30 cc.	30 cc.	10 cc.	spoonful‡	30 cc.	30 cc.	10 cc.	spoonful‡
Swallows	11	12	17	8	13	7	17	8
MIPD time	.13 (.02)	.16 (.03)	.11 (.02)	.10 (.02)	.14 (.04)	.16 (.03)	.14 (.02)	.08 (.01)
MIPD pressure	6.73 (1.18)	8.83 (.95)	6.82 (1.36)	6.25 (1.56)	8.15 (.81)	9.43 (1.07)	8.94 (1.22)	6.38 (.78)
Beginning 2MIPD time	.22 (.02)	.25 (.03)	.18 (.02)	.17 (.02)	.26 (.04)	.27 (.04)	.24 (.03)	.17 (.02)
Beginning 2MIPD pressure	4.73 (1.43)	6.17 (1.13)	4.59 (1.20)	4.13 (1.09)	6.23 (.69)	6.43 (.95)	6.59 (1.06)	4.88 (.97)
Maximum 2MIPD time	.33 (.03)	.33 (.03)	.26 (.02)	.25 (.03)	.34 (.04)	.35 (.04)	.33 (.03)	.28 (.03)
Maximum 2MIPD pressure	7.82 (1.39)	8.92 (1.02)	7.88 (1.50)	6.50 (1.55)	8.54 (.84)	8.86 (.96)	10.29 (1.74)	8.88 (1.22)
MNP time	.76 (.04)	.82 (.05)	.70 (.05)	.74 (.05)	.86 (.06)	.78 (.04)	.88 (.06)	.74 (.05)
MNP pressure	8.45 (1.56)	12.42 (1.89)	11.41 (1.85)	14.88 (3.32)	8.23 (1.39)	8.86 (2.75)	10.18 (1.92)	11.13 (2.07)
Beginning APD time	.88 (.05)	.88 (.05)	.74 (.04)	.79 (.04)	.99 (.09)	.80 (.04)	.96 (.07)	.81 (.04)
Beginning APD pressure	−6.00 (1.65)	−10.75 (2.14)	−9.88 (1.99)	−13.38 (3.88)	−7.69 (1.54)	−8.71 (2.78)	−9.47 (2.07)	−8.50 (2.28)
Maximum APD time	.92 (.05)	.94 (.05)	.77 (.04)	.84 (.04)	1.02 (.09)	.85 (.04)	1.00 (.06)	.85 (.04)
Maximum APD pressure	1.36 (.58)	1.58 (.50)	.76 (.76)	1.38 (1.36)	.85 (.44)	1.71 (.92)	.71 (1.06)	3.00 (.96)

* Expressed in seconds following the initial positive deflection.
† Figures represent millimeters of mercury above or below resting nasal pressure.
‡ Average volume 6.2 cc.
All figures are means. Those in parenthesis are the standard error of the mean.

swallowing complex; and (4) longer nasal pressure complexes were recorded in the supine position.

To determine the statistical validity of these observations, the Type II nasal pressure group was selected because its large size (504) made it most suitable for comparative study with the *t* test. Comparison

TABLE V

TEMPORAL* AND MANOMETRIC† CHARACTERISTICS OF NASAL PRESSURE CURVES WITH SWALLOWING

Type IV

	Upright				Supine			
Bolus material	Water	Watery barium	Watery barium	Barium paste	Water	Watery barium	Watery barium	Barium paste
Volume	30 cc.	30 cc.	10 cc.	spoonful‡	30 cc.	30 cc.	10 cc.	spoonful‡
Swallows	24	17	18	17	15	18	19	20
MIPD time	.14 (.02)	.14 (.01)	.14 (.03)	.14 (.02)	.16 (.02)	.16 (.02)	.14 (.02)	.16 (.03)
MIPD pressure	6.71 (.56)	8.76 (.88)	6.72 (.89)	5.29 (.58)	9.60 (1.28)	8.39 (.69)	7.00 (.81)	5.90 (.73)
Beginning 2MIPD time	.24 (.02)	.24 (.02)	.23 (.03)	.25 (.03)	.27 (.03)	.26 (.02)	.24 (.02)	.26 (.04)
Beginning 2MIPD pressure	3.63 (.55)	4.67 (.68)	4.44 (.73)	2.00 (.44)	6.60 (1.20)	5.67 (.71)	4.11 (.79)	3.30 (.64)
Maximum 2MIPD time	.36 (.02)	.35 (.03)	.33 (.04)	.36 (.04)	.39 (.03)	.36 (.02)	.32 (.02)	.36 (.04)
Maximum 2MIPD pressure	7.42 (.78)	8.41 (.98)	8.06 (.66)	5.00 (.68)	10.73 (1.70)	10.67 (1.39)	7.74 (.88)	5.70 (.65)
Beginning plateau time	.51 (.03)	.55 (.03)	.53 (.04)	.55 (.05)	.59 (.03)	.53 (.03)	.52 (.03)	.57 (.06)
Beginning plateau pressure	−1.25 (1.18)	−.18 (.93)	−.44 (.98)	−2.71 (1.08)	2.67 (1.91)	3.56 (1.41)	−.89 (.84)	−1.60 (.89)
Maximum plateau time	.66 (.05)	.71 (.04)	.65 (.05)	.66 (.05)	.74 (.06)	.65 (.04)	.68 (.04)	.72 (.06)
Maximum plateau pressure	1.33 (1.25)	3.24 (1.55)	1.28 (.90)	.18 (1.12)	4.93 (2.05)	5.56 (1.29)	2.58 (1.08)	.70 (1.03)
End plateau time	.76 (.05)	.89 (.05)	.77 (.05)	.79 (.05)	.87 (.05)	.75 (.05)	.77 (.04)	.82 (.05)
End plateau pressure	−.46 (1.28)	1.06 (1.68)	.11 (.91)	−1.76 (1.36)	2.73 (2.14)	4.06 (1.47)	.89 (1.15)	−.50 (1.06)
MNP time	.98 (.05)	1.11 (.07)	.95 (.04)	1.01 (.05)	1.14 (.06)	1.09 (.05)	.93 (.04)	.98 (.06)
MNP pressure	11.13 (1.24)	14.88 (2.19)	10.17 (1.53)	11.19 (1.59)	12.27 (1.88)	11.11 (1.48)	11.63 (1.06)	11.70 (1.55)

* Expressed in seconds following the initial positive deflection.
† Figures represent millimeters of mercury above or below resting nasal pressure.
‡ Average volume 6.2 cc.
All figures are means. Those in parenthesis are the standard error of the mean.

Table V—(*Continued*)

Bolus material	Upright				Supine			
	Water	Watery barium	Watery barium	Barium paste	Water	Watery barium	Watery barium	Barium paste
Beginning APD time	1.06 (.06)	1.21 (.08)	1.01 (.05)	1.10 (.07)	1.16 (.07)	1.12 (.05)	.96 (.04)	1.05 (.06)
Beginning APD pressure	−9.46 (1.36)	−14.41 (2.20)	−9.17 (1.69)	−8.71 (1.98)	−11.73 (1.91)	−10.11 (1.69)	−11.11 (1.05)	−10.45 (1.66)
Maximum APD time	1.11 (.06)	1.28 (.08)	1.05 (.04)	1.13 (.07)	1.21 (.07)	1.16 (.05)	.99 (.04)	1.08 (.06)
Maximum APD pressure	1.42 (.59)	1.76 (.89)	1.83 (.89)	1.47 (.89)	.53 (1.58)	.39 (.84)	1.68 (.74)	1.70 (.57)

groups were created to illustrate differences (30 cc. of water *vs.* barium paste) or similarities (30 cc. of water *vs.* 30 cc. of watery barium suspension) or to determine a specific relationship, *i.e.* the effect of volume alteration or the effect of posture change. The mean elapsed time for the maximum initial positive deflection, beginning plateau, and maximum negative pressure as well as the maximum initial positive deflection pressure and maximum negative pressure were compared within each group by means of the *t* test. The plateau was evaluated manometrically by calculating the mean amplitude (range 1.8 to 3.4 mm. Hg) and comparing these values within the identical comparison groups.

Table VI summarizes the statistical analysis of data pertaining to these observations and also includes data showing the relation between bolus consistency, nasal pressure, and time (a *t* value of 2.0 was considered statistically significant, probability = 2.5 per cent).

Pressure differences of statistical significance were infrequent. Maximum initial positive deflection was most frequently altered (5 times), whereas the plateau amplitude and the maximum negative pressure were not consistently affected by any of the variables. Although pressures were slightly higher in the supine position, this also proved to be insignificant statistically. On the other hand the number of statistically significant time differences was considerably greater and appeared to be clearly dependent on volume of bolus and position of subject (see Table VI, Groups 3 and 4). This supported the original observation that longer complexes are associated with larger volume of bolus and the supine position. Where volume of bolus was constant (Group 2) the *t* values were all low indicating similarity of the responses in the groups compared.

The effect of the variables on the duration of each of the functional phases was also studied comparatively (Table VII). The phase of oral transport had five differences of statistical significance while five were scattered throughout the remaining three phases. When bolus size was altered (Group 3), the phase of oral transport showed statistically significant differences when the subject was both upright and supine, but the subsequent phases were not consistently altered. Similar results were obtained when the effect of subject position was compared (Group 4).

Re-entry of air into the pharynx through the glottis was associated with a recognizable pressure deflection near the termination of the swallowing act in 364 tracings. In 270 of these a positive pressure trend was interposed between the maximum negative pressure and the abrupt positive

TABLE VI

EFFECT OF BOLUS CHARACTERISTICS AND SUBJECT POSITION ON NASAL PRESSURE CURVE

Comparison Group	Conditions of Comparison	Significant *t* Tests*	Conclusions
1 30 cc. water *vs.* spoonful barium paste, upright and supine	Maximum bolus variation	1. MIPD pressure upright (3.13) 2. MIPD pressure supine (4.39) 3. Beginning plateau time supine (2.27)	Significant MIPD pressure differences occur with bolus variation
2 30 cc. water *vs.* 30 cc. watery barium, upright and supine	Constant volume	All low *t*'s	Similar bolus volumes result in a similar response
3 30 cc. watery barium *vs.* 10 cc. watery barium, upright and supine	Variation of volume	1. MIPD pressure supine (2.77) 2. MIPD time upright (2.90) 3. MIPD time supine (2.31) 4. Beginning plateau time upright (2.93) 5. Beginning plateau time supine (3.39) 6. MNP time upright (3.99) 7. MNP time supine (2.71)	Dissimilar bolus volumes result in dissimilar response
4 Upright *vs.* supine: a. 30 cc. water b. 30 cc. watery barium c. 10 cc. watery barium d. Spoonful barium paste	Alteration of position	a. MNP time (2.51) b. MIPD pressure (2.31) MIPD time (2.02) MNP time (2.42) c. MIPD time (2.48) MNP time (3.73) d. None	Timing changes with position of subject Pressures are not consistently affected
5 10 cc. watery barium *vs.* spoonful barium paste, upright and supine	Change of consistency	1. MIPD pressure supine (2.37) 2. Amplitude plateau pressure supine (3.20) 3. MIPD time upright (2.22) 4. MNP time upright (2.29)	No consistent alteration is attributable to bolus viscosity

* Figures in parenthesis indicate magnitude of *t* test.

deflection. This segment, Variety A, had a mean duration of 0.18 seconds, and rose to a maximum in 0.10 seconds. The pressure during this phase increased an average of 4.6 mm. Hg to the maximal point and then declined 1.4 mm. Hg at its termination. In the remaining 94 swallows, a positive pressure deflection was superimposed on the descending gradient during the relaxation phase just prior to the maximum negative pressure. The mean duration of this segment, Variety B, was calculated to be 0.17 seconds and rose to the point of maximum positive pressure in 0.08 seconds. The pressure change during this interval was almost identical to that seen in Variety A, namely 4.7 mm. Hg from onset to termination.

Certain minor pressure tracing variations were noted in the course of record analysis (Fig. 7). On several occasions (21 subjects, 23 swallows), a negative pressure deflection occurred just before the beginning of the

TABLE VII

DISTRIBUTION OF SIGNIFICANT *t* TESTS BY FUNCTIONAL PHASE

Group	Oral Transport	Pharyngeal Transport	Pharyngeal Cleansing	Oropharyngeal Relaxation
1				
30 cc. water *vs.* spoonful* barium paste, upright and supine	—	3.27 S†	—	—
2				
30 cc. water *vs.* 30 cc. watery barium, upright and supine	—	—	—	—
3				
30 cc. watery barium *vs.* 10 cc. watery barium, upright and supine	2.90 U† 2.31 S	3.20 S	—	—
4				
Upright *vs.* supine:				
a. 30 cc. water	—	—	—	2.21
b. 30 cc. watery barium	2.02	—	—	—
c. 10 cc. watery barium	2.48	—	2.34	—
d. spoonful* barium paste	—	—	—	—
5				
10 cc. watery barium *vs.* spoonful* barium paste, upright and supine	2.22 U	—	2.25 S	—

* Average volume 6.2 cc.
† U indicates value obtained upright, S supine.

initial positive deflection. In 31 swallows (17 subjects) the initial positive deflection demonstrated an abrupt and transient loss of pressure producing a notch in the rising pressure gradient. In 6 swallows (6 subjects), the length of the A complex was so long as to stand out as an unusual variant. A positive deflection was also noted at the completion in 94 swallows (38 subjects). This occurred immediately after the abrupt positive deflection, was of very short duration, and returned to resting nasal pressure in less than 1 second. Twenty-two subjects on 46 occasions demonstrated a very rapid

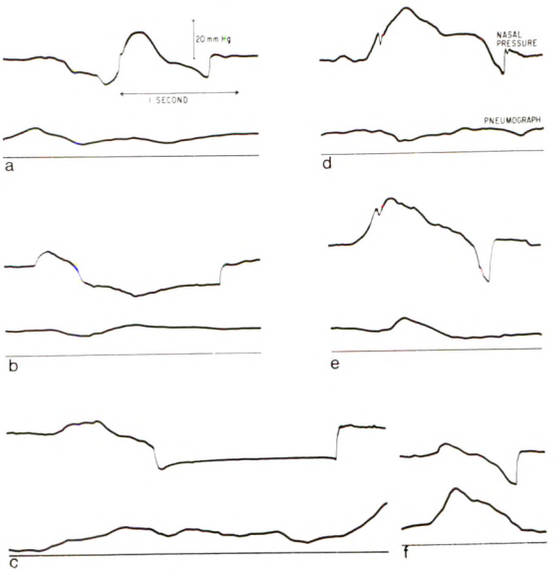


FIG. 7. Minor alterations of nasal pressure recordings are illustrated. (a) Sudden fall of resting nasal pressure prior to deglutition. (b and c) Unusually long A variants occurring after the maximum negative pressure. (d and e) Notches in the ascending portion of the nasal pressure curve; both tracings also illustrate postswallow positive deflections. (f) Unusual chest motion during swallowing with production of a pressure deflection mimicking the nasal pressure curve.

TABLE VIII

DISTRIBUTION OF SUCCESSES AND FAILURES BY BOLUS CHARACTERISTICS AND SUBJECT POSITION

1,219 Swallows

Bolus Sequence	Successes	Failures	Total	Percent Failures
Water, 30 cc., upright	149	72	221	33
Watery barium, 30 cc., upright	129	27	156	17
Watery barium, 10 cc., upright	148	23	171	13
Barium paste, spoonful, upright	80	43	123	35
Water, 30 cc., supine	109	39	148	25
Watery barium, 30 cc., supine	96	27	123	22
Watery barium, 10 cc., supine	153	16	169	9
Barium paste, spoonful, supine	76	32	108	30

chest expansion synchronous with the swallowing act in some cases mimicking the nasal pressure curve.

Analysis of the circumstances relating to unsuccessful swallows revealed an over-all failure rate of 3.1 per subject (total 279). Some subjects were especially prone to failure. One person achieved only 1 successful swallow and had 15 failures while another failed on 11 occasions but succeeded 13 times. In 3 instances subjects were excluded from the study because of a failure rate of 100 per cent. There was no correlation between failures and sex; the male and female failure rates were 23.8 per cent and 22 per cent, respectively. When multiple swallow failures were compared with technically unsatisfactory failures, no pattern that related to volume or consistency of bolus and position of subject could be established.

Table VIII demonstrates the failure rate according to bolus characteristics and subject position. It is evident that barium paste was associated with the highest failure rate in both the upright and supine positions. The 10 cc. bolus of thin barium was associated with the smallest number of failures and the lowest failure rate. In general, the failure rate was less when the subject was supine.

DISCUSSION

The present study has made it possible for us to define the characteristics of nasal pressure changes that occurred with swallowing in a large group of healthy subjects. Our previous opinion that these changes can be grouped into four basic types has been confirmed. However, we can offer no explanation about the factors that produce these four different types nor for the reasons why some subjects vary nasal pressure changes from swallow to swallow. As in our earlier study, analysis of nasal pressure changes has made it possible to divide active deglutition into four functional phases. The first of these is oral and corresponds to the classical first stage of deglutition. The classical second stage of deglutition can be further subdivided, according to our findings, into three functional components: pharyngeal transport, pharyngeal cleansing and oropharyngeal relaxation. The current research has shown that the phase of oral transport can be influenced by bolus size and subject posture whereas the subsequent functional phases appear independent of these factors. This is in agreement with the classical concept that Stage I is under voluntary control while Stage II is reflex in nature.[6] The sporadic occurrence of unusually long A varieties would indicate that palatopharyngeal separation can also be voluntarily controlled.

Review of Type I and Type III nasal pressure records reveals the frequent occurrence of a change in the slope of the negative trend. This resembles the plateau in time of occurrence and may be followed by a second negative trend. Since the fall in pressure is neither halted nor reversed, we con-

tinue to differentiate these from Type II and Type IV tracings in which a leveling or reversal of the pressure gradient occurs during the plateau. However, we feel that the point where the rapidly falling nasal pressure changes its slope, represents the beginning of the phase of pharyngeal cleansing regardless of type, and termination of this phase is indicated by a second negative pressure trend (Fig. 3 and 5).

Since variation of bolus size and subject position influence the length of the swallowing complex and the magnitude of certain pressure responses, standardization of bolus size and subject posture are mandatory in any investigation where determination of the amount of response is desired. Analysis of rates of success and failure clearly indicates that the 10 cc. bolus produces the lowest number of failures and is therefore best. Barium paste, popular with radiologists because of its excellent density and coating action, is unsatisfactory for quantitative studies because of the high rate of failures caused by unfavorable subject reaction. The shift in type distribution in the supine subjects swallowing barium paste may also reflect the distasteful consistency of this material

Table VIII bears out the impression that practice is vital in obtaining the best subject response. Bolus material is listed in the order in which it was swallowed by each subject. We believe that practice is responsible for the apparent improvement in success rate in the supine position. It is unlikely that barium paste would be swallowed more readily in the supine position at the end of an examination than 30 cc. of water in the upright position at the beginning of a study, unless practice influences performance.

The minor pressure variations (Fig. 7) noted on our records probably have no direct bearing on oropharyngeal function during swallowing but are of interest since they depict parallel and related phenomena. Knowledge of their existence is of importance to any investigator attempting to apply this method to clinical research. The preswallow negative deflection is seen after nasal occlusion and is not associated with chest movement. It probably represents some motion of the tongue or pharynx preparatory to swallowing. The small notch in the ascending pressure curve suggests a transient leak of limited volume. We believe that it is related to some specific physiologic event and speculate that it may represent opening of a communicating cavity such as the eustachian tube or a paranasal sinus. The positive pressure response after completion of swallowing originates in the respiratory tract. It probably represents some form of expiratory clearing of the airways; it does not represent the reinstitution of normal respiration. The nature of the chest motion recorded during swallowing is unexplained. It cannot be related to breathing since the orifices of the respiratory tract are closed at this time. We are unaware of any bolus related effect on chest volume that might be responsible for this change.

The similarity of nasal pressure curves under identical conditions and the changes induced by alterations of the volume of the bolus and the position of the subject emphasize the functional nature of nasal pressure curves. They provide a method for quantitative evaluation of this extremely rapid and complex stage of deglutition.

SUMMARY

Nasal pressure curves during swallowing were recorded 1,219 times in 88 healthy subjects. Of these 940 were satisfactory for analysis and could be grouped into four basic types:

Type I. An initial positive deflection followed by a smooth downward trend to a maximum negative point terminating with an abrupt positive deflection. Incidence 195 (20.7 per cent).

Type II. Similar to Type I but with formation of a plateau in the mid portion of the downward component. Incidence 504 (53.6 per cent).

Type III. Similar to Type I but with a cleft initial peak. Incidence 93 (9.9 per cent).

Type IV. A complex combining the features of Types II and III. Incidence 148 (15.8 per cent).

Nasal pressures during deglutition ranged from 32 mm. Hg above resting nasal pressure during the initial positive deflection to 34 mm. Hg below resting nasal pressure near the termination of swallowing. The duration of the nasal pressure complex was from 0.52 to 2.39 seconds, usually approximately 1 second. Statistical analysis revealed that: (1) variations in the characteristics of the bolus produced variations in the pressure and time of occurrence of events on the nasal pressure curve; (2) similar bolus characteristics evoked similar manometric and temporal responses; (3) larger volumes of bolus were associated with an increase in the duration of the initial positive deflection; and (4) longer nasal pressure complexes were recorded in the supine position.

Nasal pressure curves contained landmarks subdividing the act of deglutition into four functional phases: oral transport, pharyngeal transport, pharyngeal cleansing, and oropharyngeal relaxation. Alteration of the volume of the bolus and subject posture significantly changed the duration of oral transport, whereas the subsequent phases were unaffected by changes in size or consistency of the bolus or position of the subject. This is in agreement with the classical concept that Stage I (oral transport) is voluntary while Stage II (pharyngeal transport, pharyngeal cleansing, and oropharyngeal relaxation) is reflex in nature.

Practice under the conditions of the experiment and a bolus of 10 cc. volume are recommended to produce the lowest failure rate. Barium paste is considered an unsuitable substance for quantitative study of swallowing.

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VOL. 99, NO. 3

URETERAL PERISTALSIS IN DUPLEX RENAL COLLECTING SYSTEMS*

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PARTIAL or complete duplication of the renal collecting system is the most common congenital anomaly of the upper urinary tract.[9,13,16] It has been said that evidence of this abnormality is apparent in 2 to 3 per cent of all intravenous urographies.[6,12,13] For many years it has been taught that these conditions occur in association with a high incidence of infection, calculi, and other renal complications,[5,7] and that simple or ectopic ureteroceles[3,17] and vesico-ureteral reflux[1,15] frequently accompany complete duplication.[3,17] The present study was undertaken to determine the frequency of aberrations of dynamics that occur in association with duplication of the renal collecting system. Observations were made during cinefluorographic studies of the peristaltic activity of the renal pelvis and ureters.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

When duplication is complete, there are two ureters with two orifices in the bladder. The orifices may be close together in a single sheath or may be separated by a short distance (Fig. 1). In partial duplication (bifid ureter), the two ureters join somewhere along their course or even in the wall of the bladder (Fig. 2). In most cases of both types of duplication, the ureters cross twice, usually high near the kidney and again in the pelvis.

With the present-day degree of resolution in cinefilming, several factors have been established in regard to renal dynamics in normal subjects[2] (Fig. 3, *A–D*). Ureteral peristalsis begins after a constriction at the uretero-pelvic (U-P) junction, from which point all contrast medium in the ureter distally is milked in a single wave toward the bladder. In 12 per cent of subjects, this peristaltic wave fails to remove a small amount of contrast material, which is left in the lower third of the ureter. Constriction at the U-P junction sometimes (24 per cent) is preceded by detectable contraction of the renal pelvis and/or infundibula.

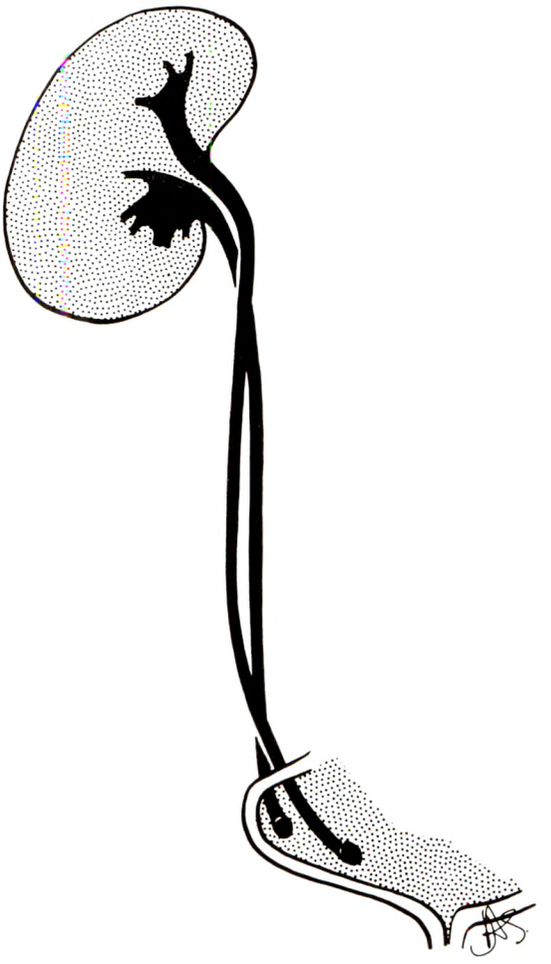


FIG. 1. Complete duplication of the renal collecting system. The upper pole ureter usually crosses the lower ureter twice and inserts low in the bladder wall.

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From the Department of Diagnostic Radiology, Royal Victoria Hospital, Montreal 2, Quebec, Canada.

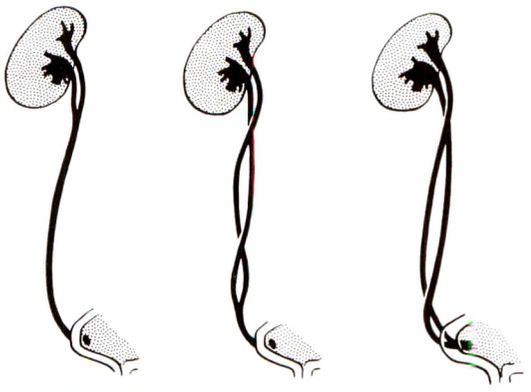


Fig. 2. Incomplete duplication (bifid ureter). The two stems join at any point along their course, even in the bladder wall.

Ureteral peristalsis originates from no other source and retrograde ureteral peristalsis does not occur.

MATERIALS AND METHODS

Studies were made of 43 patients aged 3 weeks to 68 years (mean age, 22 years); 25 had partial duplication and 18 had complete duplication of the renal collecting system. The control group comprised 75 subjects without evidence of disease of the genitourinary tract; criteria of normality were as reported previously.[2]

The subjects were not dehydrated; all were studied in the supine and prone positions and some were studied in the erect position also. Fluoroscopy was performed with an 8 inch image amplifier and orthicon television system after rapid injection (1–2 min.) of 50 ml. methylglucamine diatrizoate. Cinefluorography of peristaltic sequences was recorded at $7\frac{1}{2}$ frames per second.

The majority of patients with bifid ureter were asymptomatic and had suffered no urinary tract infection in the past; the anomaly had been demonstrated during investigation of other conditions. Three patients, however, had very severe urinary tract infection.

RESULTS

Peristalsis was asynchronous in all but 2 of the 43 patients. Those in whom peristalsis was not clearly visualized maintained some degree of drainage to the bladder, usually when in the erect position.

Partial duplication: bifid ureter (25 cases). Peristaltic waves were not detectable in any position in 4 patients despite obvious drainage to the bladder. In 17 of the remaining 21, peristalsis originated as a constriction near the upper calyx and in the infundibulum and proceeded as one milking wave toward the bladder; in 8 of these (38 per cent), the lower half of the bifid system was not seen to contract or to show antegrade peristalsis at any time. When peristalsis occurred in the lower half of the system, there was a contraction of the pelvis followed by constriction of the uretero-

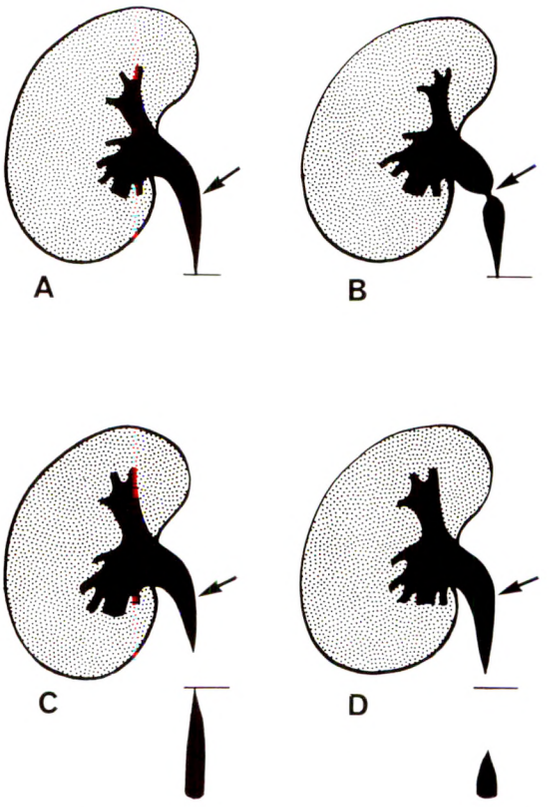


Fig. 3. Sequence of normal ureteral peristalsis. (*A*) Upper ureter filled with opaque medium. (*B*) Sudden constriction at uretero-pelvic (U-P) junction. (*C*) Peristaltic wave milking all opaque medium distal to U-P junction toward bladder. (*D*) Passive refilling of upper ureter before the arrival of the next constriction at the U-P junction and resultant ureteral peristalsis.

pelvic junction and then by ureteral peristalsis (*i.e.*, similar to normal pyeloureteral drainage).

Retrograde peristalsis (Fig. 4, *A–G*) occurred in 21 cases. This started in one "limb" as normal ureteral peristalsis toward the junction, which then appeared to activate retrograde peristalsis in the other limb, of such degree as to distend the pelvis and calyceal system of that limb. The pattern most frequently observed was of antegrade peristalsis in the upper limb with retrograde peristalsis in the lower limb. Sometimes the pattern was reversed, and in several patients both patterns were combined, one alternating with the other. When the junction of the two ureters was high (near the renal pelvis), there were other variations also. Some contractions originated with a sudden constriction at the junction of the two ureters, sending retrograde peristaltic waves into one or both ureters and a milking wave toward the bladder. A few minutes later another constriction arose at the junction and sent an antegrade peristaltic wave toward the bladder, without any retrograde movement.

Complete duplication (18 cases). The presence of double ureteral orifices in the bladder was confirmed by cystoscopy in 13 subjects. Cystoscopy was not performed in 5 subjects, but repeated intravenous urography had shown no evidence of ureteral junction and cinefluorography had depicted two separate ureters to the bladder. Retrograde peristalsis was not observed in any of the 18 subjects with complete duplication. Not infrequently, clear-cut peristaltic waves were apparent in only one of the two ureters, regardless of position. Some of the ureters showed only "wormy" peristalsis. When vesico-ureteral reflux was present, the waves subsided in the middle and lower ureter.

REPORT OF A CASE

Mrs. M.H., a 60 year old married nurse, was admitted to the Royal Victoria Hospital on April 29, 1965. Until her present illness she had experienced no urinary symptoms. Episodes of "mucous colitis" had been controlled with atropine and phenobarbital. Hysterectomy had been performed some years previously. Two weeks before her admission, a productive cough had developed; penicillin was given orally for 5 days and the respiratory symptoms cleared. A mild degree of mucous diarrhea developed, and when this cleared several days later she experienced weakness. Three days before admission, fever, urinary frequency and right back pain developed.

At the time of admission her temperature was 101° F., blood pressure 130/80 mm. Hg and pulse rate 78/min. and regular. She had vague pain and tenderness to deep palpation in the area of the right kidney. Numerous white blood cells were present in the urine, which grew *E. coli*. The erythrocyte sedimentation rate (Wintrobe) was 38 mm. in 1 hour (corrected), and the white blood cell count was 12,600/cu. mm., with a predominance of neutrophils.

The patient's temperature ranged between 101° and 103° F. On April 30, intravenous urography was performed. The following morning she was drowsy and disoriented and appeared severely ill, with respirations of 40/min., blood pressure 80/60 mm. Hg and pulse rate 120/min. There were no localizing neurologic signs. Several specimens of blood drawn at this time grew *E. coli*, sensitive to ampicillin and chloramphenicol. Treatment was instituted with chloramphenicol (intravenously) and hydrocortisone. The patient's condition improved and her temperature became normal.

The patient has been examined every 4 months since her discharge from the hospital; she has continued to feel well and laboratory investigations have yielded normal results.

Roentgen Findings. April 30, 1965. Intravenous urography performed 24 hours before the onset of clinical septicemia and shock revealed bilateral duplications and dilated ureters on the right side (Fig. 5*A*).

May 11, 1965. Cine-intravenous urography demonstrated sluggish peristalsis of both ureters on the left side, but no evidence of retrograde peristalsis. The two left ureters appeared to join in the wall of the bladder. On the right side the ureters joined at the level of the lower end of the sacrum. When antegrade peristalsis in the upper limb reached the junction, it immediately initiated marked retrograde peristalsis of the lower limb, which flooded the con-

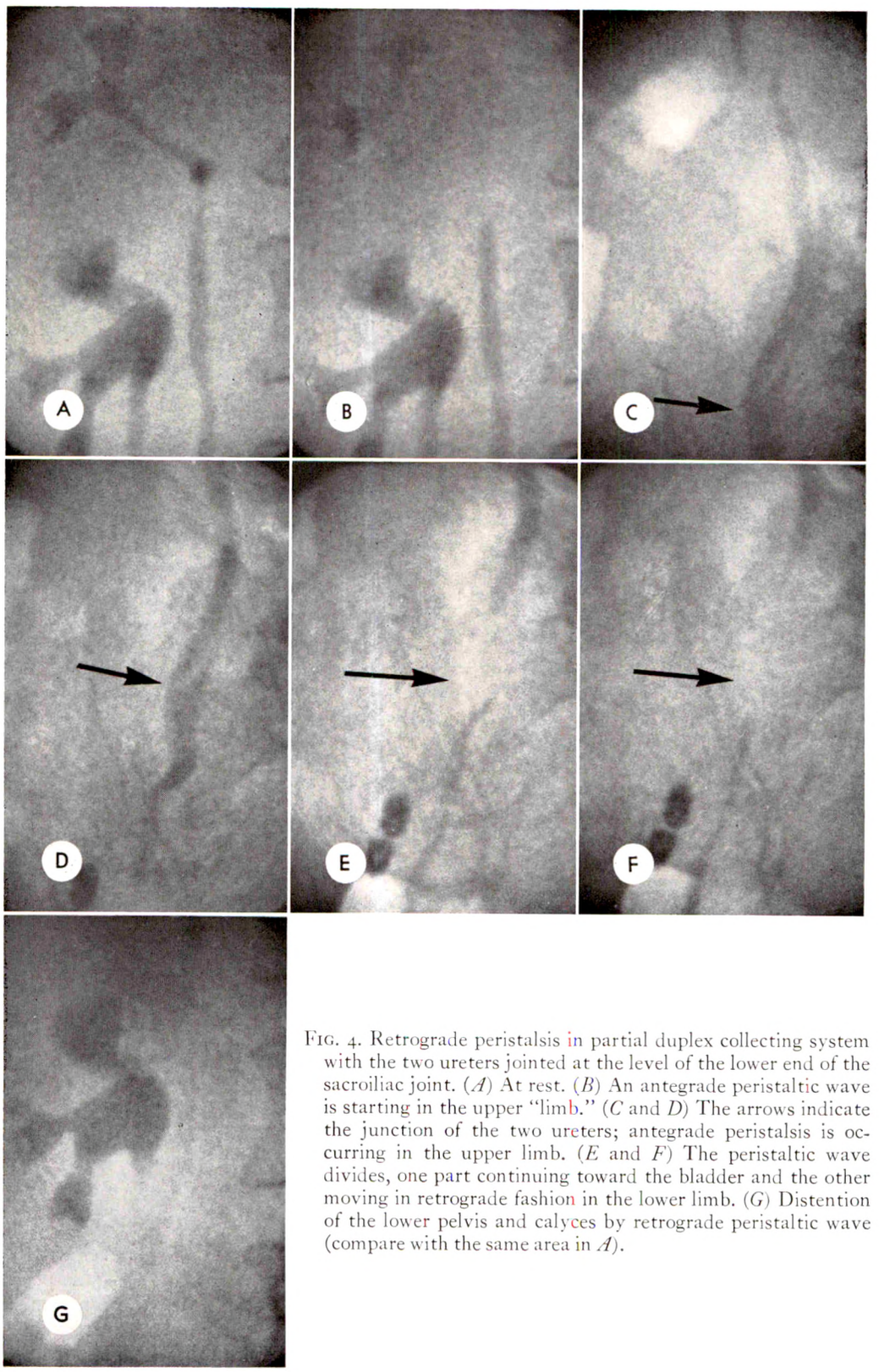


Fig. 4. Retrograde peristalsis in partial duplex collecting system with the two ureters jointed at the level of the lower end of the sacroiliac joint. (*A*) At rest. (*B*) An antegrade peristaltic wave is starting in the upper "limb." (*C* and *D*) The arrows indicate the junction of the two ureters; antegrade peristalsis is occurring in the upper limb. (*E* and *F*) The peristaltic wave divides, one part continuing toward the bladder and the other moving in retrograde fashion in the lower limb. (*G*) Distention of the lower pelvis and calyces by retrograde peristaltic wave (compare with the same area in *A*).

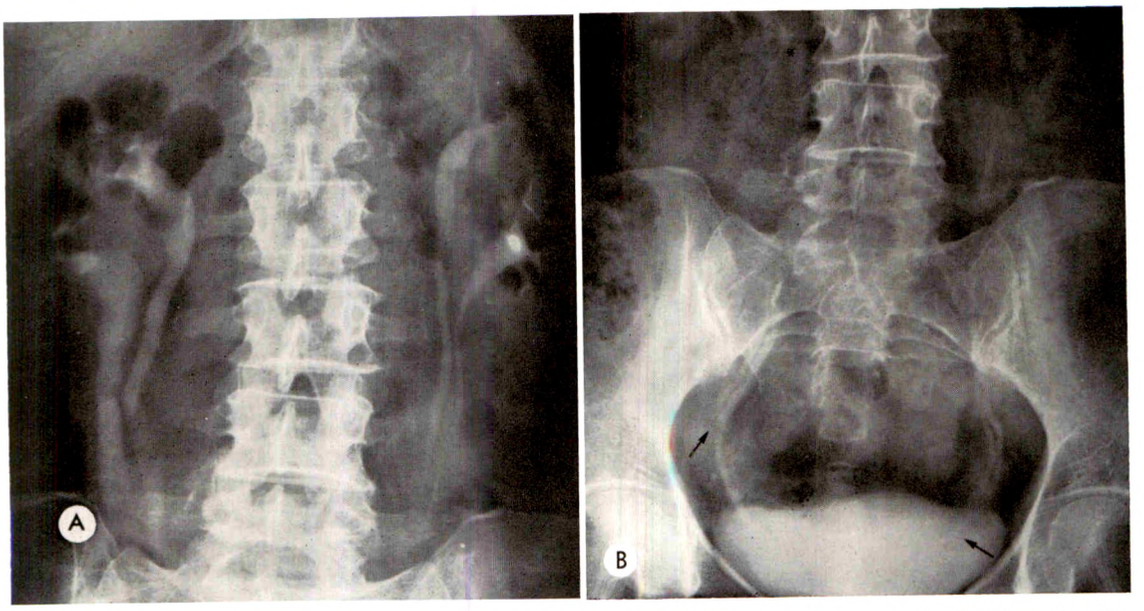


Fig. 5. *Reported Case.* (*A*) April, 1965: Intravenous urogram 1 day before the onset of clinical septicemia. Bilateral duplication; retrograde peristalsis shown in the right ureters but not in the left. (*B*) August, 1965: The ureters on the right side join in their lower third (left arrow). The ureters on the left side join in the wall of the bladder (right arrow).

trast medium back to distend the pelvis and calyceal system of the lower half of the kidney. Sometimes the process was reversed, with antegrade activity in the lower and retrograde peristalsis in the upper limb. This activity was seen when the patient was supine, prone, and, to an even greater extent, when she was erect.

August, 1965. The patient was asymptomatic and her urine was clear. An intravenous urogram (Fig. 5*B*) demonstrated the junction of the right ureters in their lower third and of the left ureters probably in the wall of the bladder. Cine-intravenous urography again showed retrograde peristalsis in the right ureter but was not very satisfactory technically.

February, 1966. Cine-intravenous urography in all 3 positions again showed sluggish peristalsis in both limbs on the left side but no evidence of retrograde peristalsis; on the right side, contraction in one and marked retrograde peristalsis in the other occurred alternately in the upper and lower limbs. An overhead roentgenogram (Fig. 6) showed the right ureters to be slightly less dilated than at the time of septicemia.

Comment. As far as is known, this patient, who has bilateral duplication of the collecting system, experienced no relevant symptoms until the age of 60 when, in the

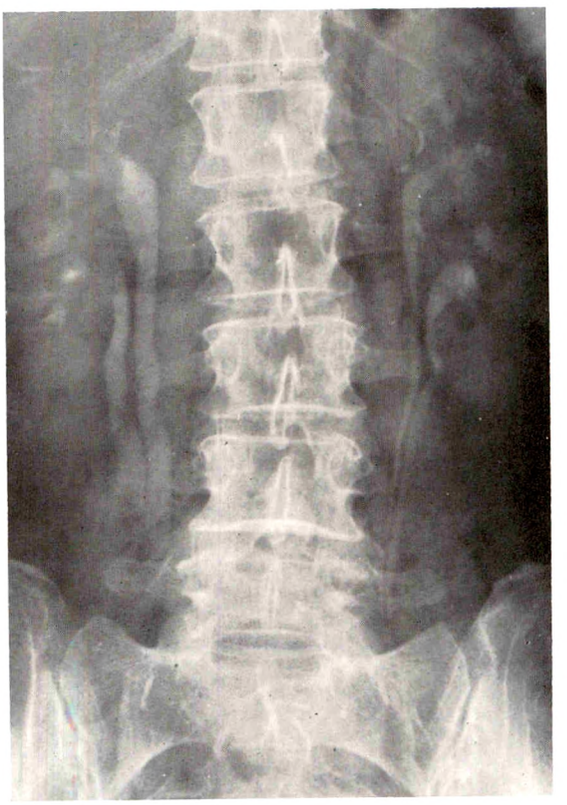


Fig. 6. *Reported Case.* February, 1966: Ten months after the initial observation the ureters on the right side are still distended.

presence of urinary tract infection, septicemia rapidly developed. It is probable that she has always had retrograde peristaltic activity on the right side and that, in the absence of infection, she was asymptomatic. Retrograde peristalsis apparently does not occur in the two left ureters, which appear to join in the wall of the bladder.

DISCUSSION

The findings obtained in the present study differed greatly from those in normal subjects.

Retrograde peristalsis was visualized in 21 (84 per cent) of the 25 subjects with bifid ureters, and it may be that this does occur at some time in all such cases. The other 4 patients, 2 of whom were re-examined several months later in various positions, showed no demonstrable peristaltic waves in any direction; however, when they were erect, contrast medium drained to the bladder and the ureters emptied slowly. Retrograde peristalsis was sometimes apparent only on the most careful scrutiny; the waves varied from weak impulses that faded before reaching the renal pelvis to powerful peristalsis that stripped contrast medium from the ureter and greatly distended the pelvis and calyces.

There were many variations in the pattern of peristalsis, although usually (but not invariably) it was the same in any one patient in all positions. The picture most often observed was of antegrade peristalsis in the upper "limb" and retrograde in the lower, but often this reversed abruptly. When the U-P junction was near the pelvis, constriction occasionally arose at the junction and sent retrograde waves into one or both limbs and some contrast material toward the bladder. The junction of the 2 limbs was not seen in all cases, even when retrograde peristalsis was apparent. When it was visualized, some of the contrast medium which had reached the junction was propelled into the distal common ureter and bladder.

Retrograde peristalsis occurred very frequently, even when patients were in the erect position. However, in such instances, and while retrograde peristalsis persisted, 5 or 6 constrictions usually drained most of the contrast material from both limbs and the common stem into the bladder.

In 1951 Campbell[4] reported that sodium iodide injected into the pelvis of one part of a bifid ureter, irrespective of whether the ureters were enlarged, appeared roentgenographically in the other pelvis. This finding has been confirmed by others[10,11,15] and has given rise to the term "uretero-ureteral reflux." There is some mixing of contrast medium at the junction, but the term "retrograde peristalsis" is preferable since this is the dominant phenomenon and since the reflux to the second limb results from the higher pressure in the antegrade (peristalsing) limb than in the other branch. The *dominant* feature of this phenomenon is the effect created by the peristaltic wave in the contracting limb, which, when it reaches the junction, triggers a stimulus for retrograde peristalsis in the other (low pressure) limb.

Although retrograde peristalsis was not seen in any of the 18 patients with complete duplication, it may occur in such cases, since stenosis or partial block of an otherwise normal ureter sometimes gives rise to this. In such cases peristalsis is normal as far as the block and then either fades, giving rise to slight dilatation of the ureter proximally, or suddenly becomes retrograde and milks all of the contrast medium back to the renal pelvis. Thus, a partially blocked half of a complete duplication could be the site of retrograde peristalsis following antegrade activity in the same ureter.

Vesico-ureteral reflux and pyelonephritis develop in many patients with duplication of the renal collecting system, most frequently in association with complete duplication. Ambrose and Nicolson[1] found infective organisms in a much higher percentage of complete duplications than bifid ureters and Stephens[15] observed vesico-ureteral reflux in the lower half of complete duplication in 75 per cent (18 of 24 ureters) and in the upper ureter in 25 per cent (6 of

24). In the latter study, vesico-ureteral reflux was not observed in 7 cases of bifid ureter, as was the case in most of our patients with bifid ureter who underwent cystography.

The case reported in the present study illustrates the fact that retrograde peristalsis probably occurs in varying degrees of severity throughout the lifetime of patients with bifid ureter and by itself probably causes no damage. However, when these patients develop a urinary tract infection (? and vesico-ureteral reflux) this usually is severe and may be very difficult to manage. During peristalsis ureteral pressure reaches 20–50 mm. Hg. It is easy to imagine the effect of bombardment by pathogenic organisms of the pelvis and calyces at this pressure during each peristaltic contraction, since the much lower pressures used during retrograde pyelography can cause pyelo-interstitial and pyelo-lymphatic backflow, and such backflow of pathogenic bacteria could result in septicemia.

When an ectopic ureter is inserted beyond the external sphincter of the bladder, complete duplication with ureteral ectopia can be treated successfully by resection of the ectopic ureter; the stump is tied off and its upper part anastomosed to the other ureter.[8,14] Swenson and Ratner[16] treated 7 cases of complete duplication by resection of the lower aperistaltic ureter (as measured by manometric pressure studies) down to 1 inch from the bladder and anastomosis of the renal pelvis to the normal upper pole ureter. Their patients had had reflux to the lower ureter and were infected, aperistaltic, and symptomatic. They were selected for this treatment as opposed to heminephrectomy because at operation they appeared to have a satisfactory renal cortex of that half of the kidney or because the other part was badly scarred. These patients had been followed up for $3\frac{1}{2}$ years; all became asymptomatic even though some were still infected. Lenaghan[10] reported 5 cases of bifid ureter with chronic infection in which it was felt that surgical treatment was necessary to eliminate "ureter-to-ureter reflux." One of the limbs of the bifid ureter was excised, together with its portion of kidney. The decision as to which segment to remove was based on the relative merits of the two parts of the kidney and the attached ureters. Infection cleared in 4 cases and a small ureteral stump which caused stasis in the fifth patient was removed later.

In cases of clinically uncontrollable infection of a bifid ureter it seems logical to construct a simple uretero-ureteral anastomosis high up near the renal pelvis, without surgical resection. In view of the findings demonstrated during the present study of renal dynamics it is reasonable to suppose that this alternative route would provide an "escape valve" for the bacteria, which then would be released into the other ureter and would partially drain into the bladder.

The present study does not bear out the suggestion of Dees[6] that bifid ureters uncomplicated by infection or stone formation cause pain due, possibly, to relative narrowing of the lumen at the point of bifurcation or incoordination of ureteral peristalsis; nor does it support the theory of Gutierrez[9] that, in crossing, the double ureters compress one another and interfere with drainage and, therefore, give rise to pain due to overfilling of ureters and pelves. Only 2 of our 25 patients with bifid ureters experienced abdominal or flank pain and both of these had severe urinary tract infection. Retrograde peristalsis in itself apparently does not cause pain.

Finally, it is interesting to comment on the asymmetry of peristalsis. Complete asynchrony of peristalsis in the two limbs was present in 41 of the 43 subjects studied. The other 2 patients presented some interesting features. When they were in the supine position, whenever the upper segment of ureter contracted while it was crossed over the lower portion high near the renal pelvis, it appeared to cause the lower ureter to contract from that point, and then the two ureters milked in unison toward the bladder. When these patients were turned into the prone or erect posi-

tion, movements became asynchronous. It is known that, during surgery, pinching of a portion of the ureter causes peristalsis, which starts at that point and which proceeds only toward the bladder. Thus, the proximity of the two ureters at their point of crossing may have constituted a similar stimulus in these 2 cases.

CONCLUSIONS

Many aberrations of ureteral drainage were observed during cinefluorographic studies of 43 subjects with partial or complete duplication of the renal collecting system. In many cases only one of the two ureters was seen to have peristaltic contraction in any position. Frequently only "wiggling" peristaltic movements were visualized, and often the uretero-pelvic junction of the upper ureter was high, near the infundibulum.

An outstanding finding was the occurrence of retrograde ureteral peristalsis in 84 per cent of the patients with partial duplication or bifid ureter. This occurred when an antegrade peristaltic wave from one limb arrived at the junction and flooded contrast medium back to the pelvis and calyceal system of the other limb. It is thought that this occurs throughout the patient's lifetime and that it is of no clinical significance except in the event of pathogenic infection, when serious and chronic infection or even septicemia may result.

The findings obtained during this study of renal dynamics indicate that simple uretero-ureteral anastomosis high near the renal pelvis would constitute a logical procedure in the treatment of bifid ureter with chronic uncontrollable infection.

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THE EXCRETORY UROGRAM IN CHILDREN WITH URETERORENAL REFLUX*

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THE problem of urinary tract infection in infants and children has been receiving an increasing amount of attention in recent years by pediatricians, pediatric surgeons and urologists. The diagnosis, evaluation and follow-up of these patients require a complete assessment by excretory urography, cine cystourethrography and gravity cystography with cystomanometric recording during filling and voiding.

In general pediatric practice, excretory urography is the initial study obtained in children with urinary tract infection, abdominal pain and failure to thrive. Therefore, it seemed appropriate to reappraise this examination for its diagnostic value in urinary tract disease.

In our institution a complete urologic evaluation consists of a history and physical examination, urinalysis, urine culture, excretory urography, cystography (gravity drip filling) with continuous pressure recording during filling and voiding, and voiding cine cystourethrography. Cystoscopic study with or without retrograde pyelography is done only when findings on the routine study require these procedures to complete the investigation, *e.g.* unilateral nonvisualization. This type of evaluation permitted us to correlate the changes on the initial excretory urogram with the final diagnosis of the patient and gave us the opportunity to appraise the intravenous pyelogram as a diagnostic means in children with urinary tract problems.

MATERIAL AND METHOD

Our pediatric surgical group has investigated a total of 925 patients from January 1, 1952 through June 30, 1966. The records of those patients having urologic evaluation during the period of January 1, 1963 through June 30, 1966 were reviewed. This yielded a total of 161 patients who manifested ureterorenal reflux by cystography or voiding cine cystourethrography. One hundred and twenty-four successive urologic patients without reflux were assessed as a control group to compare the urographic findings in children without reflux to those with proven reflux.

The excretory urograms and cystograms in the two groups were examined and any abnormalities recorded. In order to avoid any bias in such a review of films only those studies interpreted as abnormal by the original radiologist were analyzed in detail. Those studies originally recorded as negative have been listed as such in this study.

The types of abnormalities found in the excretory urogram are as follow:

1. Calyceal clubbing or loss of the normal cupping without dilatation due to scarring and atrophy of the surrounding parenchyma (Fig. 1).
2. Pyelocalyceal dilatation which varied from slight fullness to advanced dilatation (Fig. 2 and 3).
3. Ureteral changes varying from abnor-

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FIG. 1. Involvement of the superior calyx on the right due to atrophy of the surrounding parenchyma. This is typical of isolated calyceal involvement.

mally complete filling to advanced dilatation (Fig. 2 and 3).

4. Decreased size of the kidney due to chronic or recurrent pyelonephritis with scarring (Fig. 4).
5. Decreased concentration of contrast material varying from delayed excretion to total nonvisualization (Fig. 5).
6. Abnormal dilatation of the urinary bladder.
7. Ureterocele.
8. Ureteropelvic obstruction.
9. Double collecting system.

The abnormalities found in the cystogram are as follows:

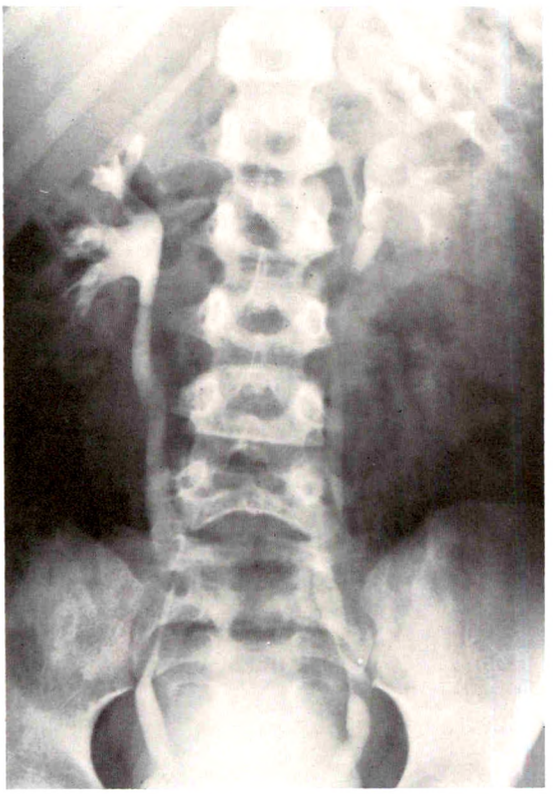


FIG. 2. Minimal dilatation of the pyelocalyceal system and ureter bilaterally.

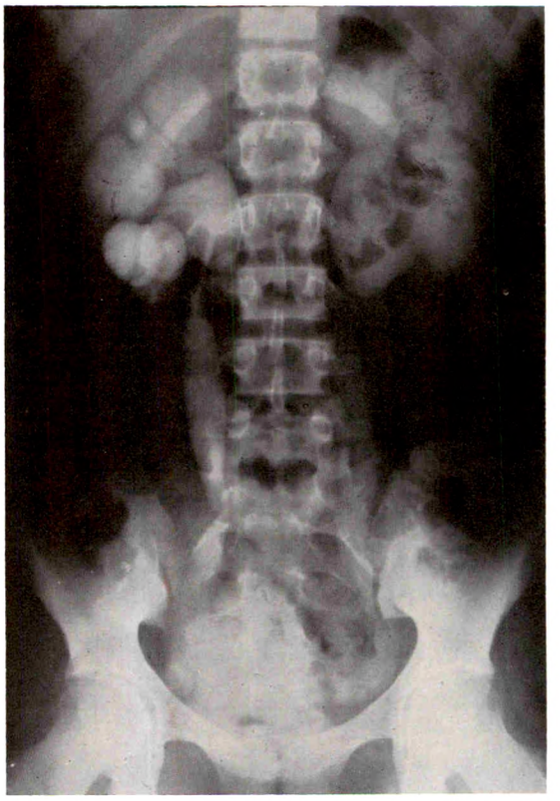
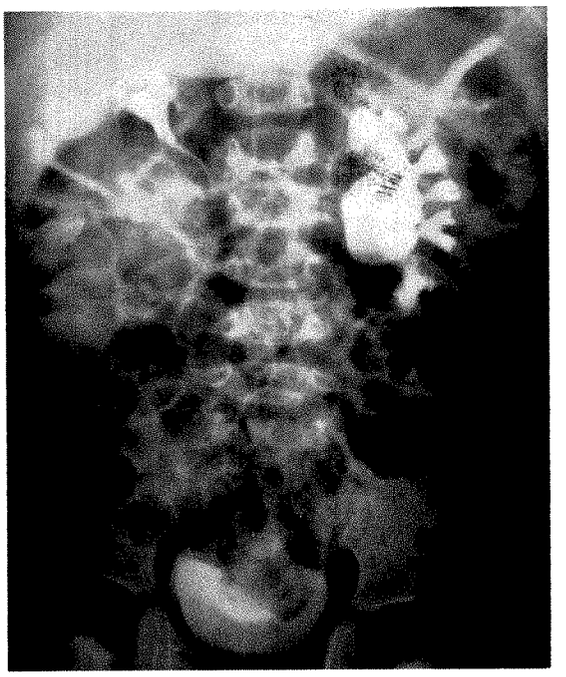


FIG. 3. Advanced dilatation of the pyelocalyceal system and ureter bilaterally.

Fig. 5. Delayed concentration of opaque medium in the lower pole of the kidney of a patient with double collecting system on the right and a ureterovesical stricture involving the ureter to the lower pole. A ureteropelvic stricture is present on the left side.



1. Vesicoureteral reflux varying from a small quantity in the ureter to massive distention of the involved pyelocalyceal system and ureter (Fig. 6 and 7).
2. Bladder neck obstruction.
3. Posterior urethral valves.
4. Stenosis of the external urethral meatus.

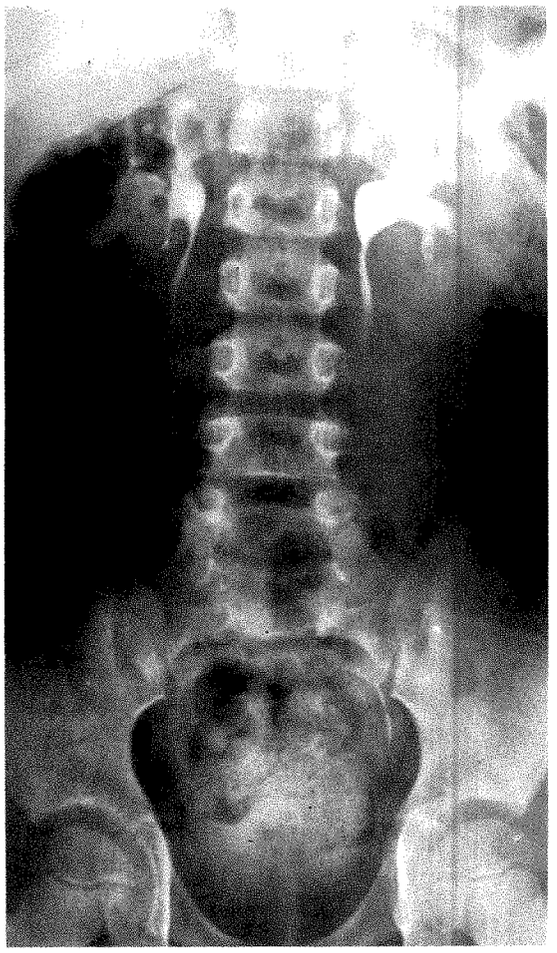


Fig. 4. Scarring and contraction of the right kidney due to infection. Note the compensatory hypertrophy of the left kidney.

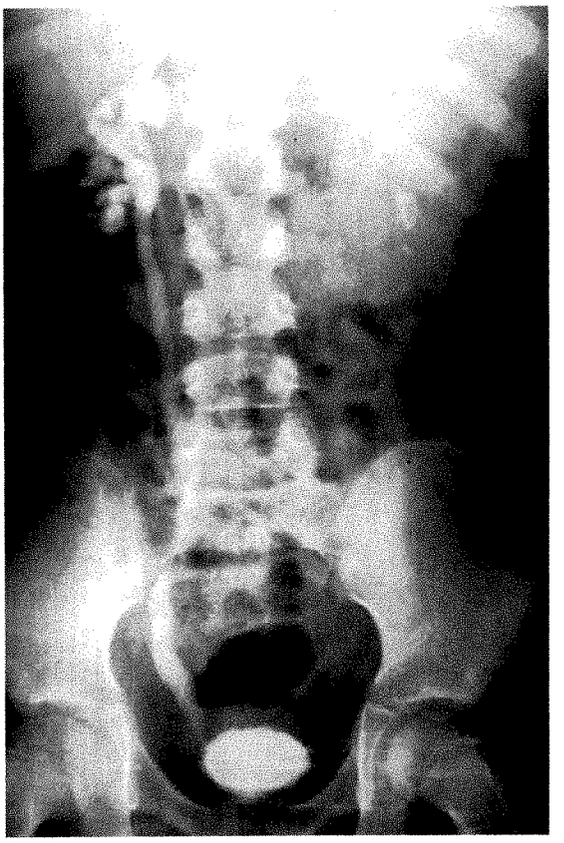


Fig. 6. Cystogram showing minimal reflux on the left side and moderate reflux on the right side.

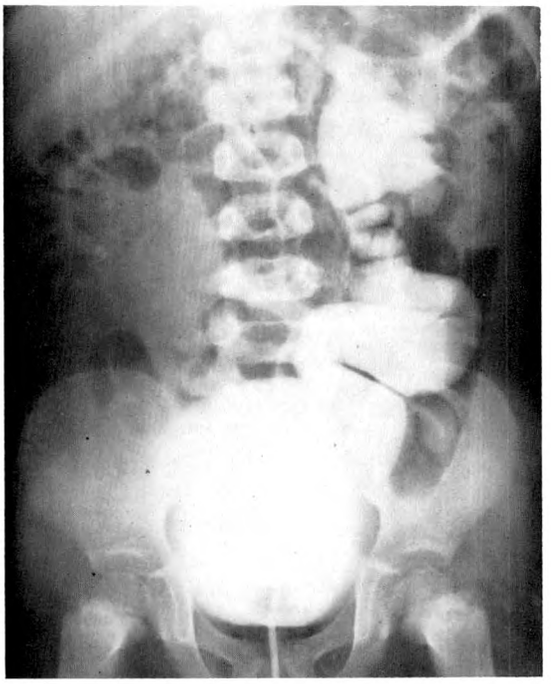


FIG. 7. Cystogram showing advanced ureterovesical reflux on the left side.

RESULTS

The patients without reflux formed one group while those with ureterorenal reflux were divided into a group of 64 patients treated medically by a voiding schedule, double-voiding and long-term antibiotic treatment and a second group of 98 patients who required surgery as part of their management. In our institution surgery is carried out only in those patients showing progressive disease with conservative medical treatment. The exceptions to this rule are patients presenting initially with clearly defined severe obstructive disease, *e.g.* posterior urethral valves, vesicoureteral stricture, ureterocele, ureteropelvic obstruction. Those cases in which bladder neck surgery was carried out were those with recurrent or unresponsive infection with persistently elevated voiding pressure. Increased voiding pressure *per se* without infection and/or progressive damage to the upper urinary tract was not a criterion for surgery.

In the medically treated group were 9 patients who did not reflux initially and 3 patients who did not have the excretory urogram and cystogram at the time of first evaluation leaving 52 patients who presented with reflux on the initial study and an excretory urogram for analysis. The surgically treated group had 13 patients

TABLE I

THE EXCRETORY UROGRAM IN CHILDREN WITH URETERORENAL REFLUX

	Patients without Reflux		Patients with Reflux Treated Medically		Patients with Reflux Treated Surgically	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Number	125		52		64	
Female	95	76.6	39	75.0	35	54.7
Male	29	23.4	13	25.0	29	45.3
Median age	5 years		5 years		3 years	
Patients 12 months and under	12	9.7	5	9.6	16	25.4
Negative intravenous urogram	69	55.6	21	40.3	6	9.5
Calyceal clubbing	3	2.4	3	4.8	9	14.3
Pyelocalyceal fullness	39	31.5	27	52.0	51	79.4
Ureteral fullness	26	20.9	18	34.6	32	49.3
Decreased renal size	1	0.8	3	5.8	5	8.0
Decreased concentration of contrast material	3	2.4	1	1.9	15	23.8
Dilatation of bladder	11	8.9	3	5.8	5	8.0
Ureterocele	1	0.8	0		3	5.0
Ureteropelvic obstruction	4	3.2	1	1.9	3	5.0
Double collecting system	6	4.8	5	9.6	13	20.6

Table II

PYELOCALYCEAL FULLNESS IN THE INTRAVENOUS PYELOGRAM

		Patients without Reflux		Patients with Reflux Treated Medically		Patients with Reflux Treated Surgically	
Minimal	unilateral	17	28(71.8%)	11	20(74.0%)	14	25(49.0%)
	bilateral	11		9		11	
Moderate	unilateral	3	6(15.4%)	2	7(26.0%)	1	10(19.6%)
	bilateral	3		5		9	
Advanced	unilateral	2	3(7.7%)	0	0	3	8(15.7%)
	bilateral	1		0		5	
Asymmetric		2		0		8	(15.7%)
Total		39		27		51	

who did not reflux initially, 3 who did not have an excretory urogram, 12 patients who had surgery prior to urography and/or cystography, 5 patients with exstrophy in which reflux appeared after repair and 1 patient who did not have both excretory urography and cystography performed in his initial evaluation. There were then 64 patients in the surgically treated group in which the initial urogram and cystogram could be analyzed.

The three groups of patients are compared in Table I. A more detailed analysis of the groups in terms of degree of pyelocalyceal fullness is presented in Table II. Table III compares the amount of reflux in

Table III

REFLUX IN THE CYSTOGRAM

		Patients with Reflux Treated Medically		Patients with Reflux Treated Surgically	
Minimal	unilateral	22	26 (50.0%)	9	17 (26.5%)
	bilateral	4		8	
Moderate	unilateral	8	15 (28.8%)	6	14 (21.9%)
	bilateral	7		8	
Advanced	unilateral	0		11	14 (21.9%)
	bilateral	0		3	
Asymmetric		0		13	(20.6%)
Reflux on cine only		11	(21.2%)	6	(9.5%)
Total		52		64	

TABLE IV

DIAGNOSIS AND SURGICAL PROCEDURE IN THE SURGICAL GROUP

Diagnosis	Surgical Procedures	Patients
Bladder neck obstruction	Y-V myotomy	18
	Y-V myotomy, ureteral reimplantation	10
	Y-V myotomy, ureterovesical mucosal flap	1
	Y-V myotomy, ureterostomy	2
Bladder neck obstruction and double collecting system	Y-V myotomy, ureteropyelostomy	1
Bladder neck obstruction and bilateral ureteroceles	Incision ureteroceles, Y-V myotomy, skin ureterostomies	1
Meatal stenosis	Meatotomy	4
	Meatotomy, ureteral reimplantation	1
Posterior urethral valve	Excision posterior urethral valve	6
Ureterovesical stricture	Excision ureterovesical stricture	1
Double collecting system	Ureteropyelostomy	3
	Heminephrectomy	2
Ureterocele and double collecting system	Incision ureterocele	1
	Heminephrectomy, Y-V myotomy, ureteral reimplantation	1
Ureterovesical incompetence with megaloureters	Ureteral reimplantation	5
	Y-V myotomy	1
	Y-V myotomy, ureteral reimplantation	1
	Ileal replacement of ureter	1
Congenitally short urethra	Urethroplasty	1
Anomalous position of ureterovesical junction	Ureteral reimplantation	1
Neurogenic bladder	Young bladder neck revision,	1
	Y-V myotomy, skin ureterostomies	1

the medical and surgical group. Table IV records the diagnosis and surgical procedure carried out in the surgical group.

Table I shows that patients who do not have reflux are quite similar to patients with reflux who are treated with medical therapy in the ratio of male to female, the median age of the patient when evaluated, and the frequency of presentation in the first year of life. The lower percentage of normal urograms and the increased signs of renal damage in patients with reflux indicate a more serious prognosis in this group of patients.

The group of patients requiring surgery appears to be quite distinct with a higher proportion of boys, a lower median age, and a large number of patients presenting in the first year of life. The small number (9.5 per cent) with a normal urogram is in striking contrast to the other two groups. The evidence of significant renal damage in the initial urogram is striking, with 8 per cent showing advanced scarring and 23.8 per cent decreased renal function—largely bilateral.

Table II compares the degree of pyelocalyceal fullness in the three groups. The first two groups have a similar proportion of minimal and moderate dilatation. The 3 patients with advanced dilatation of the pyelocalyceal system include 1 patient with a neurogenic bladder, 1 with a ureteropelvic obstruction and 1 with a ureterocele. In neither of the 2 patients with asymmetric fullness were the changes advanced.

The surgical group is quite different, with a lower percentage of minimal pyelocalyceal dilatation and higher percentage of advanced disease. The patients with asymmetric dilatation of the pyelocalyceal system include 3 in which one side showed

advanced changes. This totalled 11 patients or 21.6 per cent of this group presenting pyelocalyceal fullness in the urogram.

Table III compares the degree of reflux found in the medical and surgical group. In not one case did the reflux exceed a moderate degree in the former, while in the latter a significant number had advanced reflux. The asymmetric group contained 4 patients with advanced reflux on one side bringing the number to 28.1 per cent of the 64 surgically treated patients with reflux.

DISCUSSION

The excretory urogram appears to be of great significance in evaluating the child presenting with urinary tract infection. In that group of patients with reflux who required surgery in their management, less than 10 per cent had a negative study on the basis of the original report. The urogram in patients without reflux was negative in over half of the cases, and in those patients with reflux treated medically slightly more than half the studies showed some abnormality.

It would seem that the excretory urogram can be of great assistance in indicating how extensive the initial evaluation of a child with a urinary tract infection should be. Urography is an examination available in the community hospital while cystomanometry, cystography, and voiding cine cystourethrography are more commonly available in a pediatric medical center. Our findings indicate that a child aged 4 years or more with a normal urogram could be treated medically with antibiotics and a voiding schedule and followed by repeat urography in 3 to 6 months. However, any child showing advanced disease urographically (advanced pyelocalyceal dilatation, delayed or absent excretion of contrast material, renal or calyceal scarring) or any child in the first year of life should have a complete urologic evaluation in the initial phase since such patients have a high incidence of serious urinary tract pathology requiring surgical intervention as part of their management.

SUMMARY

Correlation of the findings on the initial intravenous urogram was carried out in 124 children without vesicoureteral reflux and in 116 children with vesicoureteral reflux. The urograms were abnormal in 90.5 per cent of those patients with reflux who required surgery in their management.

The abnormalities are analyzed and the usefulness of the urogram in directing initial management of the child with a urinary tract infection is discussed.

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FOUR PHASE NEPHROTOMOGRAPHY IN THE DIAGNOSIS OF RENAL CYSTS AND TUMORS*

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NEPHROTOMOGRAPHY combines intravenous aortoangiography with tomography of the opacified kidneys. The history of this procedure has been covered in previous publications.[8,9,10] Its major use has been in the differential diagnosis of renal masses, because neoplasms typically produce abnormal vascular patterns or "stains" while cysts are seen as radiolucent defects in the nephrogram. The largest series reported to date suggest an accuracy approaching 95 per cent.[3,4,5,14]

In this report our modification of the procedure originated by Evans *et al.*[5] is described and our diagnostic accuracy with that of others is compared.

PROCEDURE

Two physicians perform venipunctures using No. 13 needles in arm veins. On signal, both physicians *rapidly* inject a bolus of 50 cc. of 75 per cent hypaque.* Attention is then directed to obtaining roentgenograms of the "four phase nephrotomogram."

FIRST PHASE (AORTOANGIOGRAPHIC PHASE)

Study No. 1. We estimate the time for this exposure at 14 to 18 seconds.† The purpose of this study is to obtain a roentgenogram at the moment the aorta is opacified (Fig. 1). If aortography and/or renal angiography is the primary reason for the examination, a rapid cassette device is used to obtain diagnostic studies. But, if differential diagnosis of a renal mass is the major concern, rapid *manual* cassette change is employed, there being no urgency to demonstrate the aorta. A good aortogram is obtained in half of the examinations and a "fair" aortogram (*i.e.*, demonstration of the distal aorta only) in 21 per cent. Successful aortography depends on a 100 cc. bolus of contrast material, coordination of injections, and good timing of the exposure, with emphasis on the latter. In our experience there is little contrast difference between 75 per cent and 90 per cent hypaque.

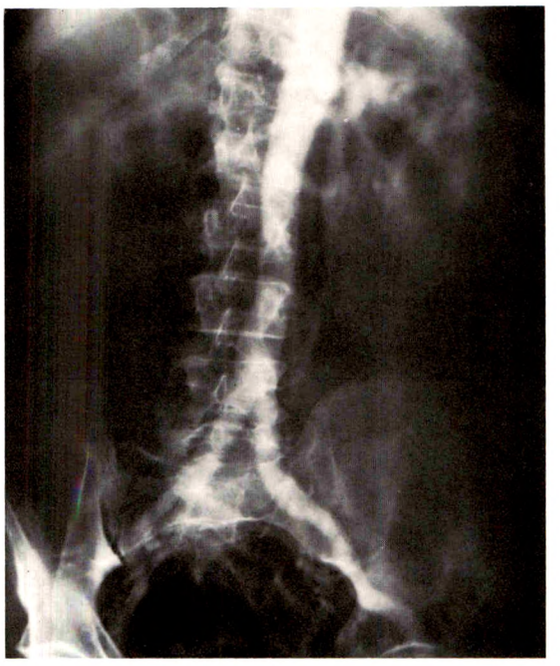


FIG. 1. Roentgenogram made at moment of aortic opacification.

* Originally 90 per cent hypaque was used, but 75 per cent compares favorably with the former in contrast, and its lesser viscosity allows easier, quicker injection. The contrast agent is warmed to expedite faster infusion. Unless one is immediately successful in venipuncture, the 90 per cent solution tends to become quite viscid, complicating injection.

† We have used both decholin (whose end-point is subjective) and I^{131}HSA (whose end-point is objective) to establish a timing of 14 to 18 seconds as adequate for most studies.

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TABLE I

DIAGNOSTIC CRITERIA

	Renal Cyst	Renal Malignancy
Vascularity of the Mass	Avascular	Hypervascular
"Zoning"	Radiolucent zone in good nephrogram	Radiopaque zone in good vascular phase
Edges of the Mass	Thin, smooth, and sharply defined	Thick, irregular
Arterial Phase Pattern	Vessels are displaced around the mass	"Tumor vessels" and "pooling" of contrast material in irregular abnormal vascular channels
Arteriovenous Aneurysms	Usually none	Often visualized
Metastases	None	Frequent in bones, lung, brain, liver (Fig. 2*B*; and 3*B*)

SECOND PHASE (NEPHROGRAM)

Study No. 2. This exposure is made as quickly as the first cassette can be manually changed. Its purpose is to obtain a study of the renal parenchyma, opacified by contrast material in the smaller vessels and tubules.

THIRD PHASE (NEPHROTOMOGRAPHY)

Study No. 3. This exposure is made as quickly as the previous cassette can be manually changed. Its purpose is to visualize by tomography the opacified renal parenchyma. The laminagraphic level is based on tomography studies made prior to the injection, and usually results in "cuts" at the 7 cm. and 9 cm. levels from table top.

Study No. 4. Another tomogram is made as quickly as the previous cassette can be manually replaced. This roentgenogram is made 2 cm. anterior to Study No. 3, and attempts to encompass any extrarenal projection of a mass.

FOURTH PHASE (FOLLOW-UP EXCRETORY UROGRAM)

Study No. 5. A plain roentgenogram of the abdomen is made at 5 minutes.

Study No. 6. A tomogram is made at 10 minutes to demonstrate the opacified collecting system at the level determined as ideal on the previous studies.

Study No. 7. An oblique roentgenogram is made on the side best demonstrating the suspect kidney.

Study No. 8. This study is made in the opposite oblique position.

Study No. 9. An upright abdominal film is exposed at 20 minutes. This is the final study and may be omitted if the results of the previous films are conclusive.

The studies made in the fourth phase often approach retrograde pyelograms in terms of quality.

DISCUSSION

Nephrotomography has been proven safe and useful in the diagnosis of renal masses.

In this series, no case of urticaria, anaphylactoid reaction or death occurred.

Other procedures are used to opacify the renal arteries and parenchyma, the best of which appears to be selective renal angiography.[8] Nephrotomography, however, avoids arteriotomy and its possible complications, and may be used before, or instead of, selective angiography. It is particularly useful in the poor-risk patient.

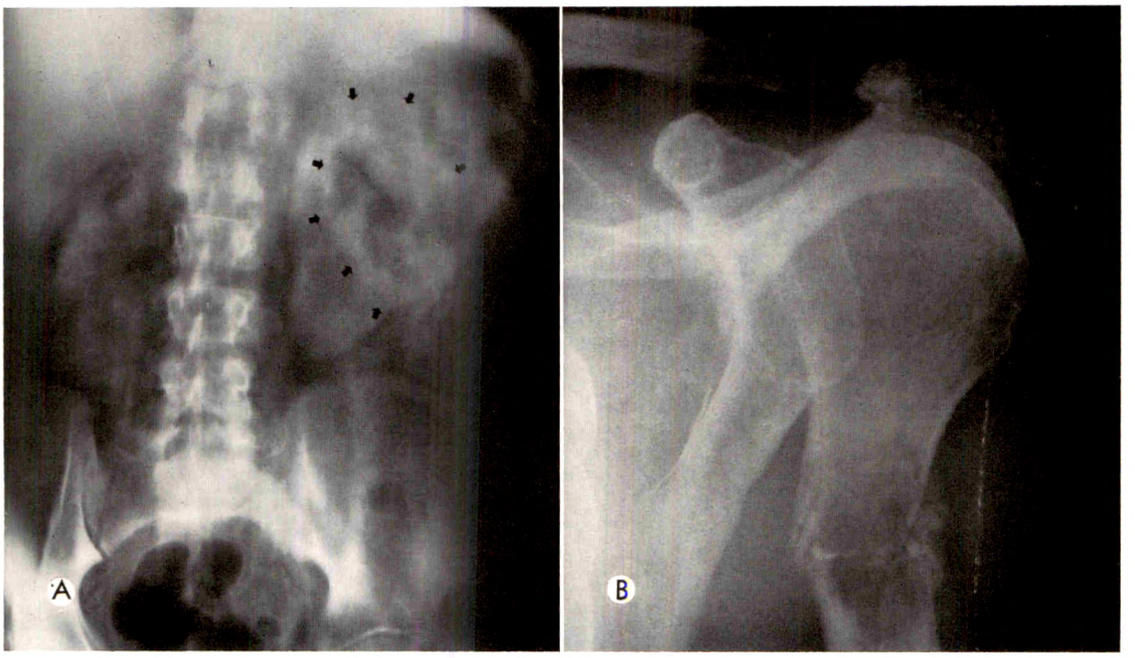


Fig 2. (*A*) Renal carcinoma of left upper pole. Hypervascularity and "staining" are apparent. (*B*) Same patient. Pathologic fracture of left humerus.

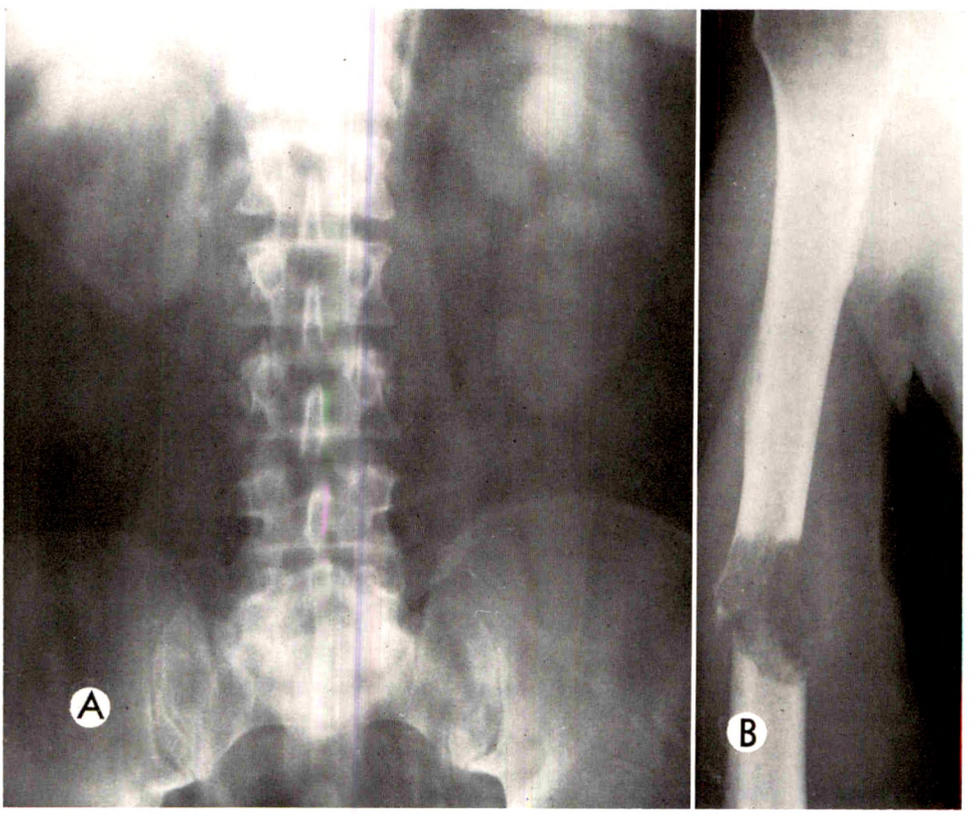


Fig. 3. (*A*) Renal carcinoma, right upper pole. There is hypervascularity and "staining." (*B*) Same patient. Metastatic carcinoma to the right humerus.

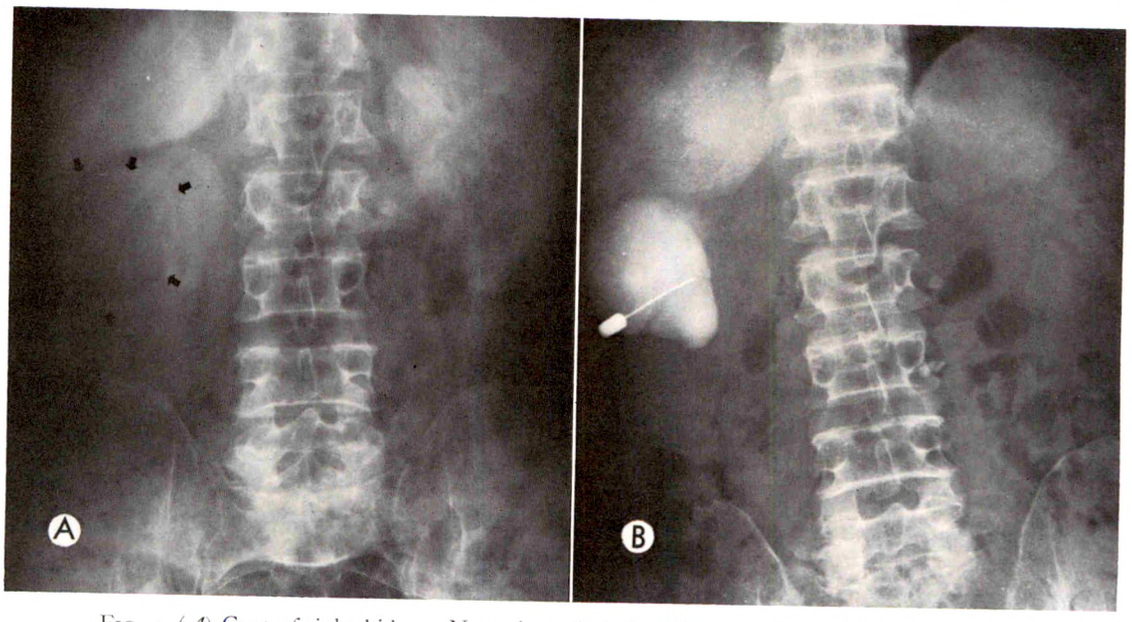


FIG. 4. (*A*) Cyst of right kidney. Note the well-defined lucent defect in the nephrogram. (*B*) Same patient after injection of contrast material into the cyst.

DIAGNOSTIC CRITERIA

Certain positive criteria for nephrotomographic diagnosis of renal masses have been established, a summary of which is listed in Table 1. The fact that neoplasms cause definite changes in the vascularity of the affected kidney (Fig. 2*A*; and 3*A*) together with other signs produced by the tumor itself (Fig. 2*B*; and 3*B*) is in contrast to the fact that cysts tend to displace vessels and produce radiolucent defects in the opacified renal parenchyma, because they are avascular (Fig. 4, *A* and *B*; and 5).

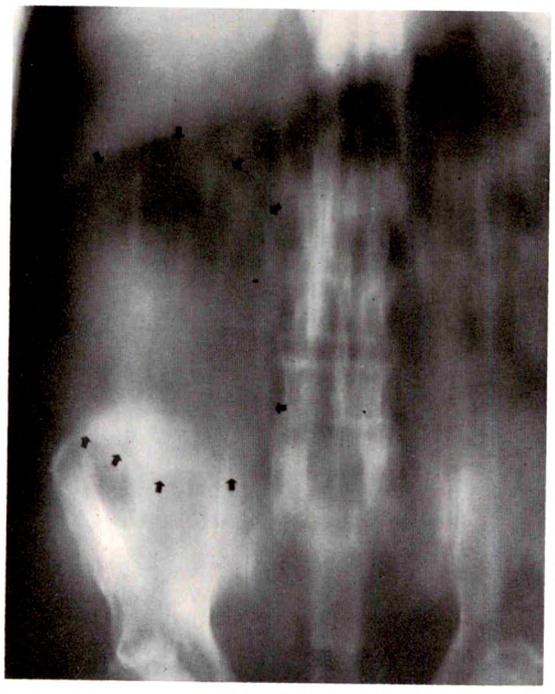


FIG. 5. Large, thin-walled cyst of right kidney. Tomography best outlines the wall.

Because of these differences, the more rigidly one demands satisfaction of all established criteria, the more likely is a correct diagnosis possible. Since a neoplasm is the more important lesion, it is best to consider as malignant any lesion which does not satisfy all criteria for a cyst. Errors in this series arose from a tendency to interpret as renal cell carcinoma those borderline changes which later proved to be cyst. Nevertheless, we believe it best to err toward the diagnosis of malignancy.

Despite the shortcomings of the procedure, accuracy in reported series of 94 per cent is not uncommon. In the remaining cases the differential diagnosis cannot be established, and renal angiography or surgery *should be recommended.*

The clinical picture is frequently so similar in patients with cyst or tumor that,

with the exception of evidence of metastatic disease, signs and symptoms are not reliable in differential diagnosis (Table II).

SERIES EVALUATION

A total of 276 patients had 302 examinations. The average age was 55.8 years with an age span of 21 to 81 years. Two patients were female.

The indications for the examination were (1) differential diagnosis of a renal mass suspected on a previous excretory urogram or by physical examination, or (2) investigation of hematuria or hypertension.

Significant findings in 108 cases other than renal cyst or tumor included abdominal aortic aneurysm (Fig. 6; and 7, *A* and *B*), crossed renal ectopia, retroperitoneal neoplasm, etc.

A diagnosis of renal neoplasm was made in 32 patients. At surgery, 3 of these patients had renal cysts. A total of 27 had surgery, 2 refused surgery, and other disease prevented surgery in 3.

Thirty-two patients were diagnosed as having renal cysts; 22 were operated on and 2 had renal cell carcinoma (Fig. 8). These two errors were the most serious in this study. Of the 10 patients not having surgery, 2 refused surgery and 8 showed no evidence of metastatic disease after 3 years.

Of 115 patients diagnosed as having a "normal" study, later follow-up, surgery or autopsy revealed renal malignancy in 4.

Our accuracy is compared with that of others in Table III.

TABLE II

COMPARISON OF CLINICAL SYMPTOMS AND SIGNS IN RENAL CYST VS. TUMOR[2,8]

	Renal Malignancy (per cent)	Renal Cyst (per cent)
Hematuria	50	33
Pain	46	44
Mass	13	22
Fever of Unknown Origin	7	0
Leukocytosis	7	0
Hypertension	13	11
Metastases	23	0

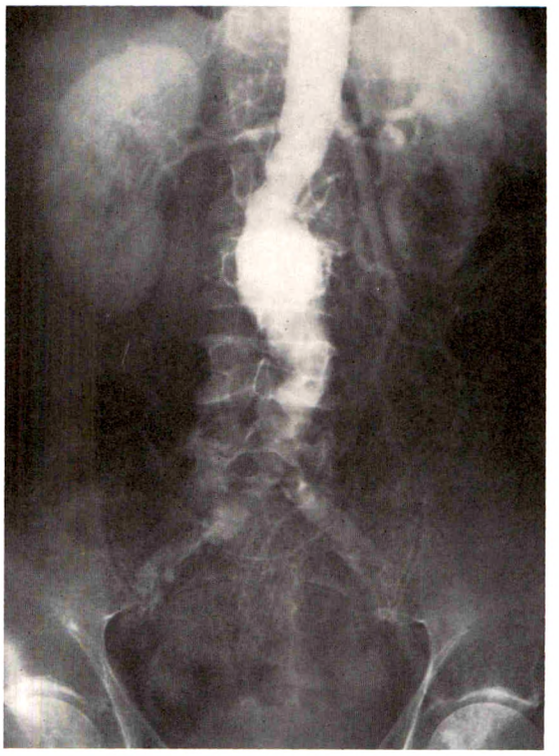


FIG. 6. Unsuspected aneurysm of the abdominal aorta.

SUMMARY

Four phase nephrotomography is a safe and useful examination in the differential diagnosis of renal masses. It can be performed in any radiologic department which has a tomographic apparatus. Its reliability is directly related to the experience of the interpreter and the persistence with which he demands satisfaction of all established positive roentgenographic criteria. Negative criteria have a doubtful place in the differential diagnosis of renal masses.

Four phase nephrotomography is valuable because: (1) poor-risk patients may safely be examined by this special procedure, possibly avoiding surgery; (2) accuracy of the procedure is reproducible from one institution to another in the range of 90 to 95 per cent; (3) it avoids arteriotomy; and (4) its differential diagnostic yield is excellent.

About 5 per cent of patients cannot be diagnosed by this method.[6] If four phase

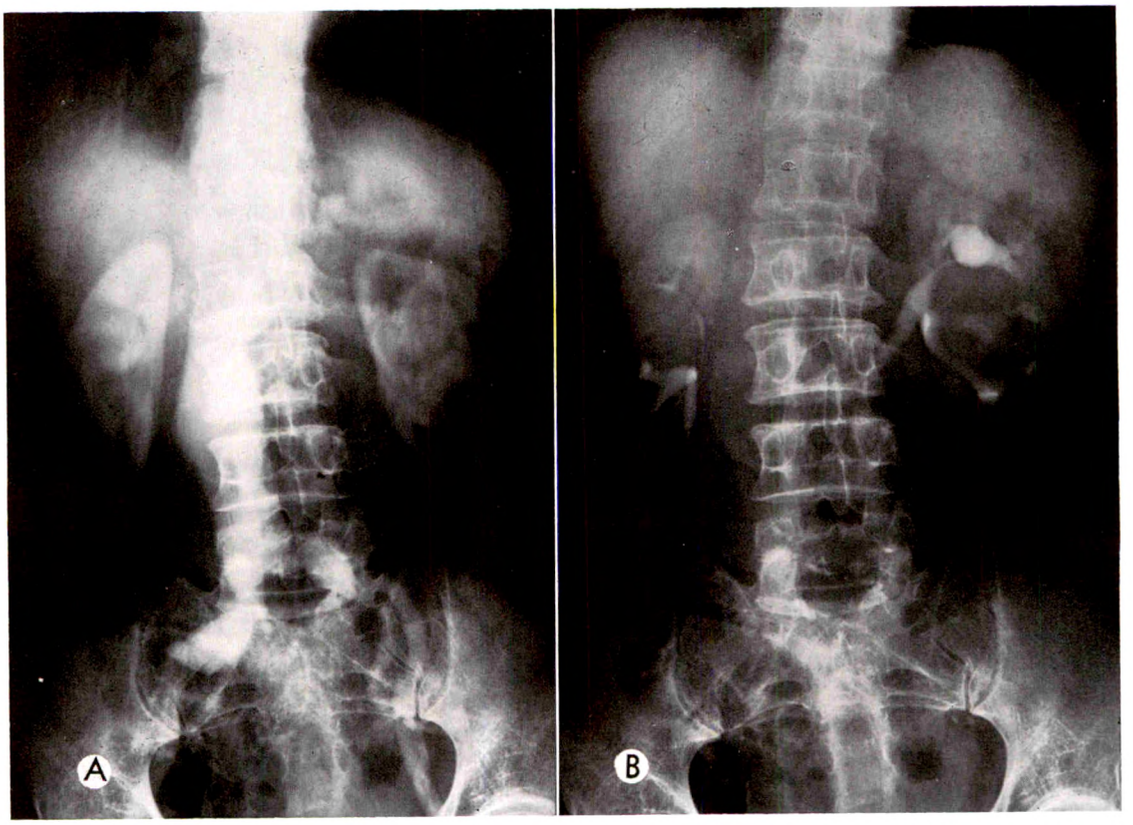
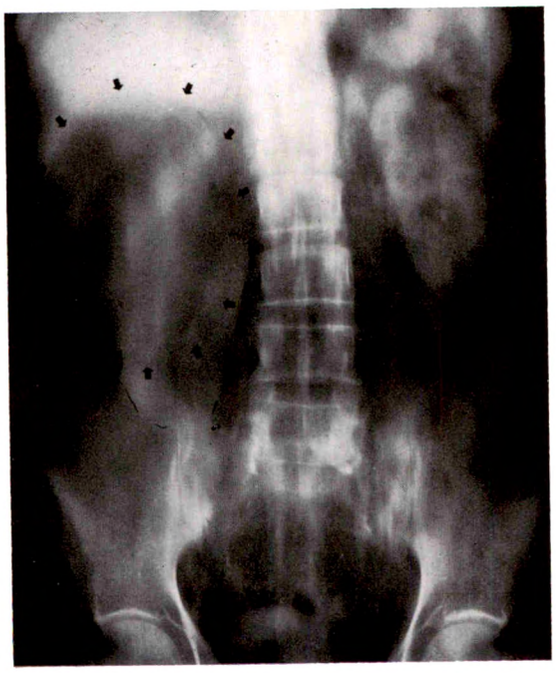


FIG. 7. (*A*) Unsuspected aneurysm of the abdominal aorta and its branches. The well-defined cyst in left kidney appears hypervascular due to adjacent bowel gas, demonstrating one of the diagnostic pitfalls in interpretation. Similar changes are noted on the right sided nephrogram. (*B*) Same patient. Follow-up excretory urogram demonstrating the caliceal deformity caused by the left renal cyst. A double collecting system can be seen on the right.



nephrotomography results in inconclusive findings, retrograde femoral aortography or selective renal angiography is recommended.

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FIG. 8. These roentgenographic findings met all the criteria for a cyst: thin wall, clear demarcation, radiolucency. However, a renal carcinoma which had undergone cystic changes due to necrosis was found.

TABLE III

COMPARISON OF THIS STUDY WITH OTHER RECENT SERIES

	Present Study	Chynn and Evans[3]	Witten *et al.*[14]	Evans[4]
No. of Patients	276	500	300	252
Diagnosed As Tumor	32	77	38	44
Incorrect	3	5	4	3
Per Cent Error	9.4	6.5	10.5	6.8
Diagnosed As Cyst	32	240	147	115
Incorrect	2	13	2	5
Per Cent Error	6.2	5.4	1.4[a]	4.3
Diagnosed "Normal"	115	127	79	93
Incorrect	4	5	0	4
Per Cent Error	3.5	4	0[b]	4.3
Series Error (no. of errors/no. of patients × 100)	3.3	4.6	6	4.8

[a] Nine of 147 cases came to surgery, 2 of which had carcinoma; 127 were accepted as having benign disease, without operative proof or aspiration.

[b] There were no known errors in those reported as "normal." However, 20 examinations were reported as "equivocal" or "indeterminate" and later this group of patients was proved to have 9 cysts and 5 carcinomas. These 14 cases are compared in the "series error" computation.

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AN EVALUATION OF COBALT 60 ROTATIONAL TELETHERAPY EQUIPMENT*

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THE purchase of costly radiation therapy equipment carries with it, in the mind of the user, expectations of performance usually based on the given specifications.

In 1962, a prototype rotational cobalt 60 teletherapy machine was installed at our institution for routine clinical use. Shortly, it was found that the source head flopped back and forth in the yoke as the machine rotated about its axis. In addition, it was soon discovered that the yoke rotated with respect to the main C-arm during rotational movement of the machine about the axis. With a few months of use, this became intolerable even for routine radiation therapy.

While searching for a solution to these equipment problems, it was deemed prudent to learn if similar problems existed in the equipment of other radiologists. This report is concerned with the findings of a study of 22 rotational cobalt 60 teletherapy machines in the eastern United States. The parameters which were evaluated included:

1. Measurements of movement of the central ray away from the axis of rotation in the plane of the beam.
2. Measurement of relative amounts of strain in the various components of machine; *i.e.*, yoke supporting the source head, the main C-arm and the head supporting mechanism.
3. Variation in radiation output at central ray with different areas of beam.

METHODS AND MATERIALS

The area in the plane of rotation through which the central ray always passes throughout a revolution can be described as the isocenter. It is desirable that the isocenter be a point for precise beam direction. In order to determine the amount of deviation of the central ray from the axis of rotation as a cobalt 60 teletherapy unit revolves, a

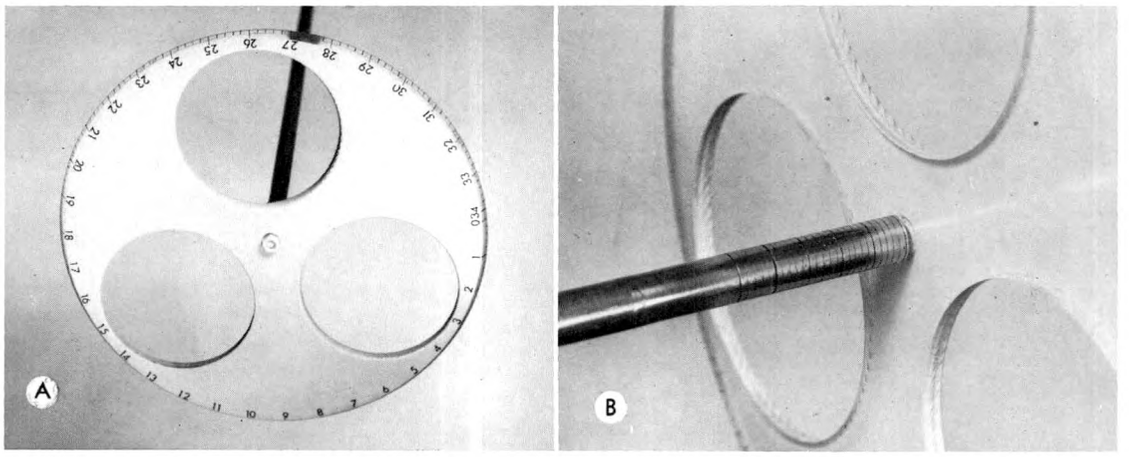


FIG. 1. (*A*) Face of protractor: scale for locating isocenter in plane perpendicular to axis of rotation. (*B*) Mounting rod of protractor: scale for determining shift of isocenter along axis of rotation.

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Supported in part by the American Cancer Society.

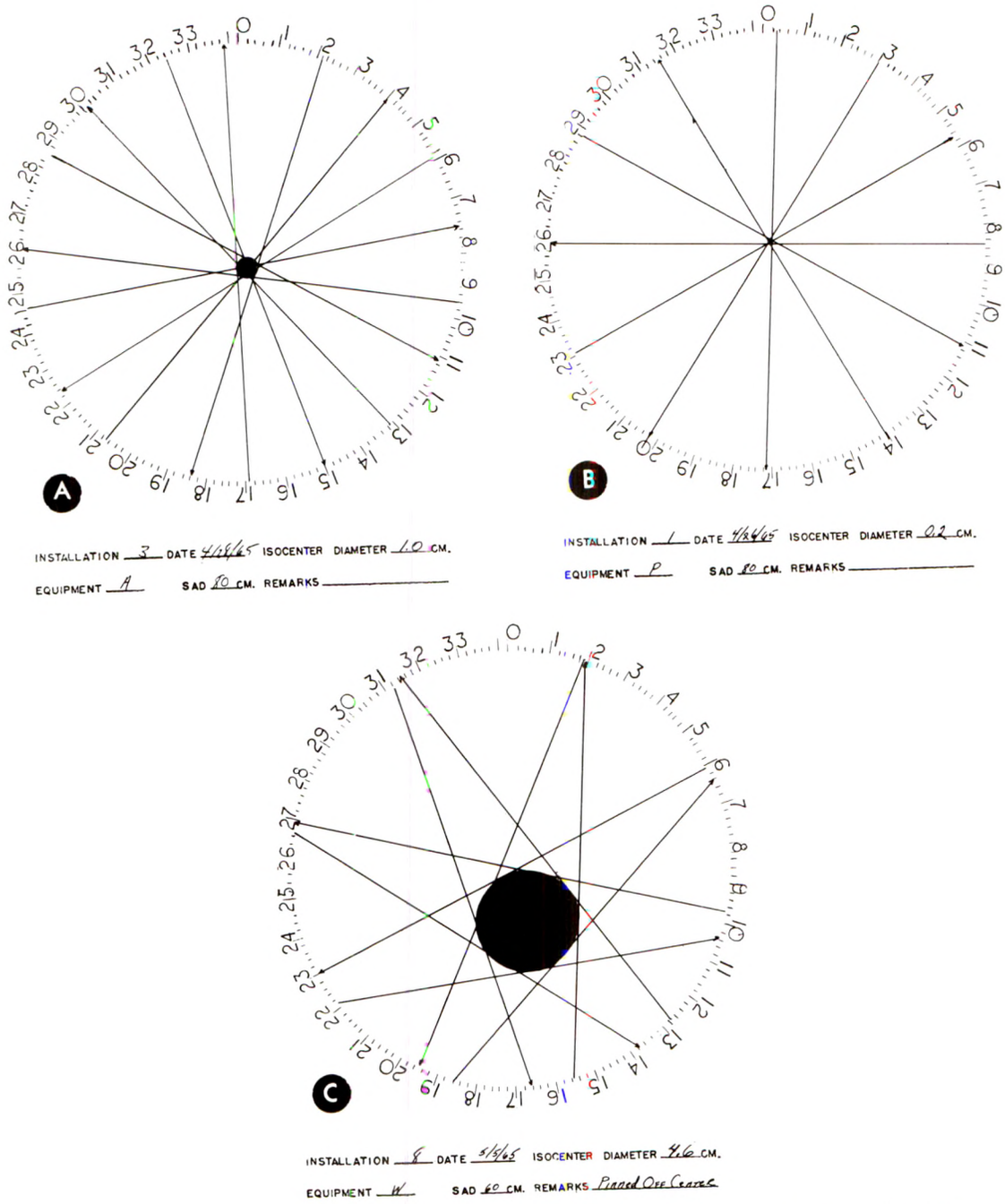


Fig. 2. Examples of isocenters. (*A*) Typical isocenter. (*B*) Small isocenter. (*C*) Large isocenter.

means was needed for accurate measurement. A large circular protractor attached to a mounting rod was constructed with arbitrary units marked along its circumference. The protractor is shown in Figure 1, *A* and *B*. It was made from $\frac{1}{4}$ inch plexiglass, 10 inches in diameter, and beveled on the edge to facilitate reading in a darkened room. Equal divisions were marked along the bevel and numbered. In use, the protractor is positioned with its center near the axis of, and in the plane of, rotation.

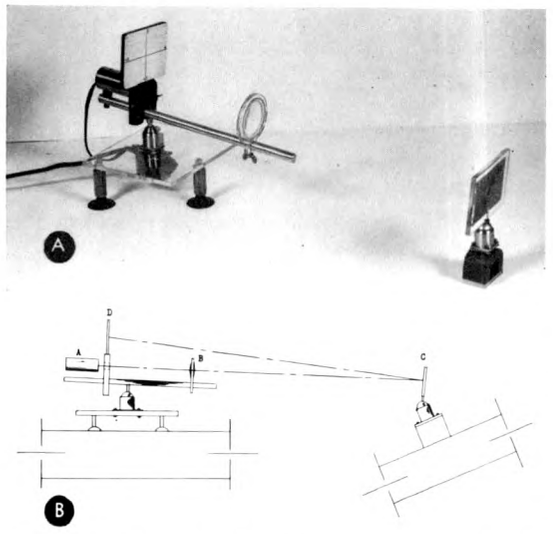


Fig. 3. Strain measuring system. (*A*) Actual. (*B*) Schematic. A = light source; B = focusing lens; C = reflecting mirror; D = coordinate grid.

The projection of the cross hairs from the beam localizer light casts a shadow on the beveled edge of the protractor at the point of entry and point of exit. These points can be used to orient the beam direction in plotting the data on a scale of the protractor drawn on paper. Entry and exit positions of the beam can be determined at intervals of 20 degrees through a complete revolution. After plotting these data from each position, the diameter of the isocenter is determined from the smallest circle that can be drawn through which all lines pass. A scale (Fig. 1*B*) marked on the support rod of the protractor is used to determine the amount of deviation of the central ray along the aixs of rotation. Some examples of typical, small and large isocenters are shown in Figure 2, *A*, *B* and *C*. The amount of deviation, or the diameter of the isocenter, is determined by two conditions: (1) the relative movement due to shifting of one member of the structure with respect to another, and (2) the amount of flexing within each member as the unit is rotated. In order to determine the weak points in a unit, measurements were made to evaluate the movement of one member relative to another. Figure 3, *A* and *B* shows the principle used to make these measurements. A light source (A) mounted on one member is directed to a mirror (C) mounted on the

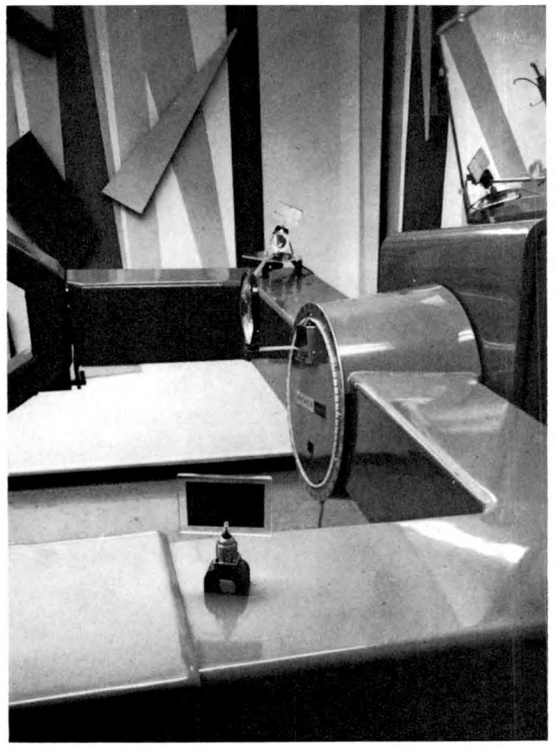


Fig. 4. Strain measuring system in use.

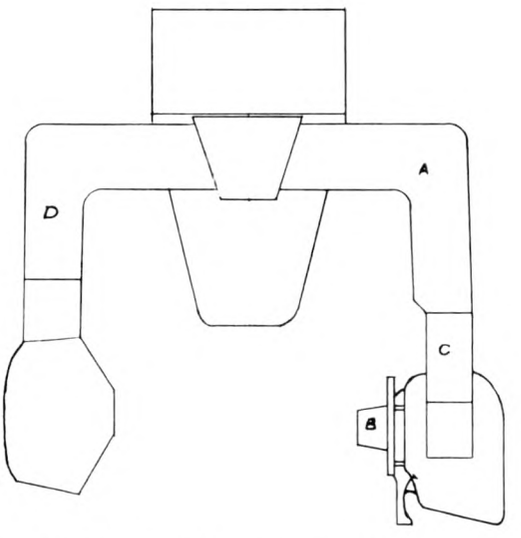


Fig. 5. Typical positions used for strain measurement. Top view of cobalt 60 unit in horizontal position. A = position of light on arm; B = position of mirror on collimator; C = position of mirror on yoke; D = position of mirror on opposite portion of arm.

second member. The light and mirror are directed in such a way that a point in the light beam is focused by a lens (B) to be seen on a screen (D) attached to the light source. The screen is marked off in grid coordinates and the location of the point image is noted. Upon rotating the machine to a new position relative motion between the two members will cause a change in location of the image. This motion can be expressed in degrees by measuring the path of light and the amount of deflection. The tangent of the angle is the image deflection divided by path length. Figure 4 shows the system mounted with the light and screen on the upper portion of the C-arm and the mirror on the lower portion. For the sake of comparison for the various units measured, the light was mounted on the upper portion of the C-arm with the mirror located successively on the head, yoke and lower C-arm as illustrated in Figure 5. To minimize errors caused by movement of the measuring system, the light and screen were mounted by rubber suction cups and held in position by use of a web strap. The mirror was attached to a magnet and remained fixed during rotation. To verify that no shift of the light source or mirror was measured, only data which could be duplicated by successive trials were accepted.

The variation in radiation output with different field sizes was determined by using an ionization probe mounted axially in the beam. The probe was connected to a roentgen rate meter. The axial position of the probe was chosen to eliminate stem effect due to exposure of varying amounts of the stem as field size changed. Measurements were made at the axis of rotation for field sizes ranging from the smallest to largest for each collimator.

RESULTS

VARIATION OF BEAM CENTER FROM ISOCENTER

Plots re-creating the relation of the central ray to the isocenter during rotation were made for each machine evaluated. The data show a range of isocenter circles from 4 mm. in diameter to 46 mm. in diameter. Some of the equipment evaluated had been altered by the addition of a pin and seat device to immobilize any "slop" between the source head and the main C-arm. Curiously, the equipment with the greatest deviation from isocenter had been "pinned" off center. The diameter of the isocenter circle for each machine studied is recorded in the central column of Table 1.

TABLE I

MAXIMUM DEVIATIONS

Installation		Diameter of Isocenter (mm.)	Deflection of Members		
			A-B	A-C	A-D
1	P	3	48′	41′	6′
2	W	18	35′		26′
3	A	10	15′		
4	P	6	27′	11′	7′
5	W				
6	W	12	21′	21′	11′
7	P	12			
8	W	46	30′	15′	19′
9	P	6	31′	23′	12′
10	W	10	48′	24′	1°38′
11	P	16	23′	33′	9′
12	A	5	27′	36′	18′
13	W	38	55′	27′	59′
14	A	4	16′	20′	28′
15	A	6	10′	6′	14′
16	A	5	23′	26′	22′
17	P	10			
18	A	8	13′	11′	19′
19	A		52′	48′	
20	P	17	53′	48′	
21	P		35′		
22	P	1	24′	28′	8′

A = Head Arm.
B = Collimator.
C = Yoke.
D = Barrier Arm.

STRAIN BETWEEN COMPONENTS OF EQUIPMENT

The study with light beam and mirror revealed a surprising amount of strain in the various parts of machines during rotation. The maximum deflections between the top of the vertical part of the C-arm and the collimator, between the top of the vertical part of the C-arm and the yoke and between the top of the vertical part of the C-arm and the barrier arm, respectively,

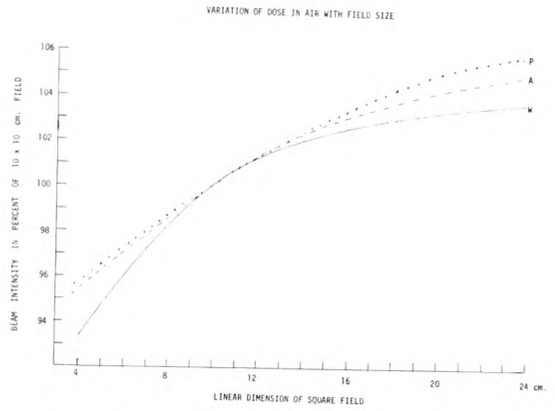


FIG. 6. Variation of dose in air with field size.

are recorded in the columns at the right of Table 1. For reference, strain giving a deflection of 25′ is equivalent to movement of the central ray of 5 mm. at a distance of 75 cm. The data demonstrate that there may be considerable re-orientation of the beam during rotation due to strain within components as well as movement between components.

VARIATION IN OUTPUT WITH DIFFERENT FIELD SIZES

Measurements of beam output are seen to vary depending on the area of the beam. Basically, the smaller the area of the beam, the lower the measured intensity. Since this variation is due largely to the configuration and design of the collimation system, the amount of variation found was somewhat specific for each manufacturer's equipment. However, within each brand, some variation was found from machine to machine. Average data from this part of the study are presented in Figure 6. Central beam intensity at the source axis distance for a 10×10 cm. field is considered 100 per cent. Intensities of beam with other areas are related to the 10×10 cm. area value as per cent. Most machines show approximately 10 per cent variation in beam intensity between minimum field size and maximum field size.

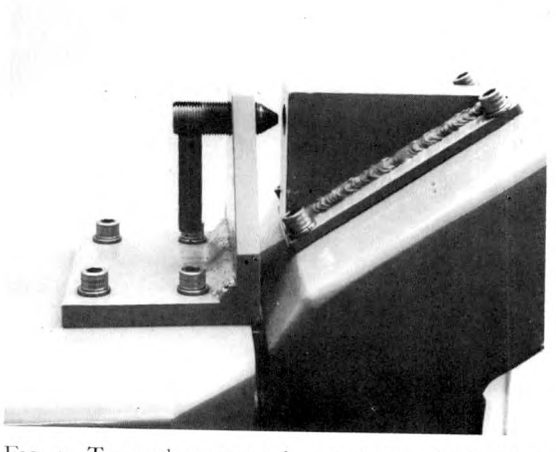


FIG. 7. Tapered screw and seat device for locking central ray to axis of rotation.

DISCUSSION

If one proposes to practice precision radiation therapy, one requires predictably precise equipment. Predictability of precision must be gained from measurement of the specific equipment in use.

A majority of the deviation of the central ray from the point of rotation stems from mobility in the linkage between the source head and the C-arm. A lesser amount of deflection is due to strain in the C-arm. In equipment which utilizes a large ring for mounting of the head and barrier, a rather substantial amount of mobility was found which was not present in the C-arm type of machine. In designing equipment which has available motion between the source head and the C-arm, it seems that manufacturers have been unable to achieve the objective free of slop. In the field, it has been learned that this problem can be solved easily and inexpensively with a tapered screw and seat device to immobilize the head-arm linkages (Fig. 7). Additionally, by this means, the central ray is effec-

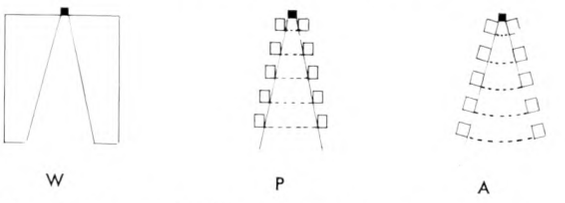


FIG. 8. Types of collimator configuration. Installation W: *Fixed cone*, 60 cm. source skin distance. Installation P: *Linear movement*, multivane, 80 cm. source skin distance. Installation A: *Curved movement*, multivane, 60 and 80 cm. source skin distance.

tively locked on the axis of rotation. This latter feature is essential when the equipment does not utilize a primary barrier as a counter weight. In recent years, the strength of the C-arm and other members of the equipment has been made sufficient to minimize strain. Strain does not appear to be a major problem at present in the C-arm type of machines.

When one seeks the ideal in the matter of beam area *vs.* beam intensity, one is seeking a constant intensity regardless of area. Essentially this may not be attained since scatter from the edges and surfaces of the collimator is always present. The amount of the scatter contribution is dependent, in part, upon the configuration of the collimator.

The types of collimator configuration in machines tested are indicated in Figure 8. These correlate with the curves in Figure 6. The relationship between beam intensity and beam area is complex and has not been given the attention the matter of penumbra has received. In part, at least, this relationship depends upon: (1) size of source and nature of side shielding; (2) alignment of source with collimator; (3) orientation of the inner surfaces of the collimator with respect to the edge of the beam; (4) variation in transmitted penumbra; and (5) presence or absence of satellite penumbra trimming devices.

CONCLUSION

It is obvious from this study that one must calibrate output for each beam area used. The competence of the installation of the equipment in this respect is extremely important. This is critical work and needs to be accomplished by persons knowledgeable in the matters which critically affect function. More of this sort of evaluation of equipment by users will be of real value.

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CAPNOSPLENOPORTOGRAPHY*

ASSESSMENT OF PORTAL VEIN PATENCY IN DOGS WITH CARBON DIOXIDE GAS

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SPLENOPORTOGRAPHY with conventional radiopaque contrast agents provides limited information concerning the patency of the portal vein in severe portal hypertension. Portal vein thrombosis is occasionally suspected but is rarely demonstrated radiologically because the contrast medium is swept away via collateral vessels. At the present time no single diagnostic examination can constantly demonstrate patency or thrombosis of the portal vein. The diagnosis may be inferred by additional studies (transhepatic portal venography, celiac axis and superior mesenteric arteriography, and direct surgical portal venography).[1,5,7,8,13]

The authors describe a new method of roentgen examination of the splenoportal venous system using carbon dioxide, which was chosen because of its "safe" properties.[4,11,14] *Capnosplenoportography* (Greek *kapnos:* smoke) is an appropriate term for this technique. This examination was tested in dogs under normal and simulated pathologic conditions.

The possible clinical applications of the technique are briefly discussed.

MATERIALS AND METHODS

Twelve mongrel dogs with an average weight of 15 kg. were given intravenous anesthesia of pentobarbital sodium (30 mg./kg.). A midline epigastric incision was made. This surgical approach exposed the spleen for needle punctures for contrast injections. Six control examinations were performed using 60 per cent methylglucamine diatrizoate (1 cc./kg.) and 12 studies with carbon dioxide gas (2–3 cc./kg.). Six examinations were done in 2 dogs using carbon dioxide gas (5 cc./kg.).

Serial roentgenograms were made with a Schönander unit at 2 per second for 10 seconds and at 1 minute interval for 10 minutes. Initially, different positions (recumbent anteroposterior, left posterior oblique and left lateral) were used with a vertical roentgen-ray beam. A left lateral decubitus position was used with a horizontal roentgen-ray beam. A few spot roentgenograms were also made in the Fowler's position. After some trials, the left posterior oblique position was found to be the most suitable. This elevated the liver and lowered the spleen, according to the physical property of the buoyancy of gas in a liquid medium. Superimposition of the portal vein on the lumbar spine was also eliminated.

Pathologic conditions were induced with the same midepigastric incision. The portal vein was either partially or completely ligated to simulate portal vein thrombosis. In 5 dogs, 11 splenoportographies were performed using 60 per cent methylglucamine diatrizoate and 11 with carbon dioxide gas. Portal venous hypertension was artificially induced by connecting a saline infusion under pressure to a catheter inserted into the portal vein. In 2 dogs, 6 splenoportographies were made using positive and 6 employing negative contrast media.

Other physiologic parameters were also investigated. Splenic pulp pressures were made in the control and induced patholo-

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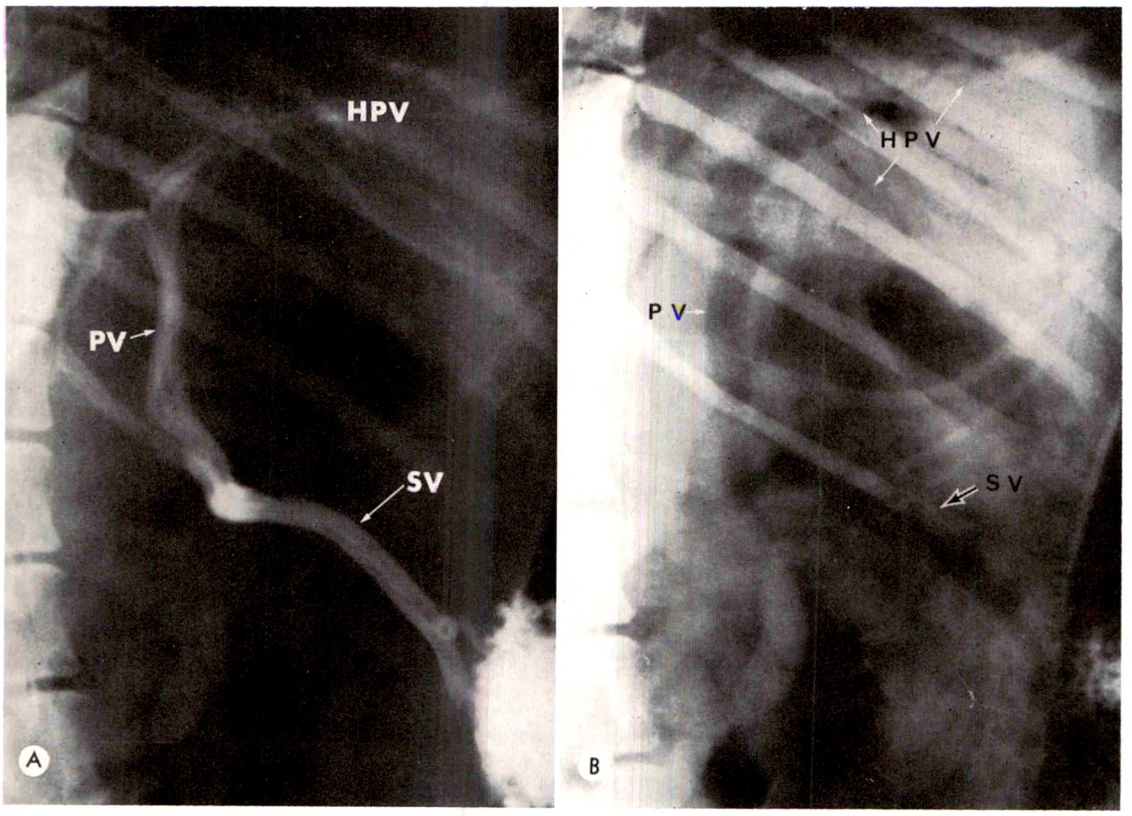


Fig. 1. *Normal.* Conventional splenoportogram using 60 per cent methylglucamine diatrizoate (*A*) and splenoportographic study using pure carbon dioxide gas (*B*) of a normal dog in the left posterior oblique position. The splenic vein (SV), portal vein (PV) and intrahepatic portal venous radicles (HPV) are well visualized. Note streaming defects in *A* and not in *B*.

gic conditions. Blood samples were taken from the right atrium for the determination of pH, pO_2, and pCO_2. In these dogs, there was continuous monitoring of the carbon dioxide content of the expired air. Liver function tests (serum glutamic pyruvic transaminase and bromsulphalein) and pathologic studies of the liver and spleen were performed.

RESULTS

Visualization of the splenoportal venous system by carbon dioxide gas (2–3 cc./kg.) in the normal dog was similar to a normal splenoportogram using radiopaque contrast media (Fig. 1*A*). The splenic vein was seen draining into the portal venous system. No streaming phenomenon was observed. Other veins were not visualized (Fig. 1*B*), but excellent delineation of the intrahepatic portal vein radicles was obtained. The optimum time of visualization of the portal vein was 2–4 seconds from the beginning of injection. Only traces of gas were seen in the intrahepatic ramifications of the portal vein in 8–10 seconds. At the end of 1 minute, carbon dioxide gas was no longer perceptible in the splenoportal circulation.

With a partial obstruction to the portal vein, splenoportography with radiopaque iodinated contrast material showed the contrast up to the site of obstruction (Fig. 2*A*). There was inconsistent visualization of the portal vein proximal to the ligature. When seen, there was delayed and poor to fair visualization of the portal vein due to dilution of the contrast material. However, utilizing carbon dioxide, the proximal and distal aspects of the obstruction were readily seen (Fig. 2*B*). In addition, the

portal venous system as well as collateral veins were also visualized. The duration of the examination was not prolonged and the time of optimal visualization of the splenoportal veins was similar to the normal (2–4 seconds).

Artificially induced portal hypertension via the pressurized saline infusion was effective in raising the splenic pulp pressure from 135 to 245 mm. saline. Under this condition, there was considerable dilution and delay of passage of the contrast material through the portal vein resulting in its poor visualization (Fig. 3*A*). Mixing and streaming defects were observed and could be interpreted to represent thrombosis of the portal vein (Fig. 3*B*). However, carbon dioxide splenoportography showed patency and excellent demonstration of the portal vein (Fig. 3*C*).

Gas analysis of the right atrial blood in dogs given 2–3 cc./kg. of carbon dioxide into the splenic parenchyma demonstrated no significant changes in the blood pH, pO_2 and pCO_2. There was no appreciable change in the carbon dioxide content of the expired air and in the state of respiration. This is in accordance with the nonvisualization of hepatic veins and correlates very well with the observations[12] that such a dosage of carbon dioxide is within the physiologic variation of normal activity. When the dose was increased to 5 cc./kg., the hepatic veins were seen and there was minimal hyperpnea. Liver function tests (serum glutamic pyruvic transaminase and bromsulphalein) showed no change with the use of carbon dioxide gas splenoportography.

COMMENTS

Iodinated aqueous and oily solutions (hypaque, renografin, ethiodol, thorotrast, etc.) have been used in splenoportal venous

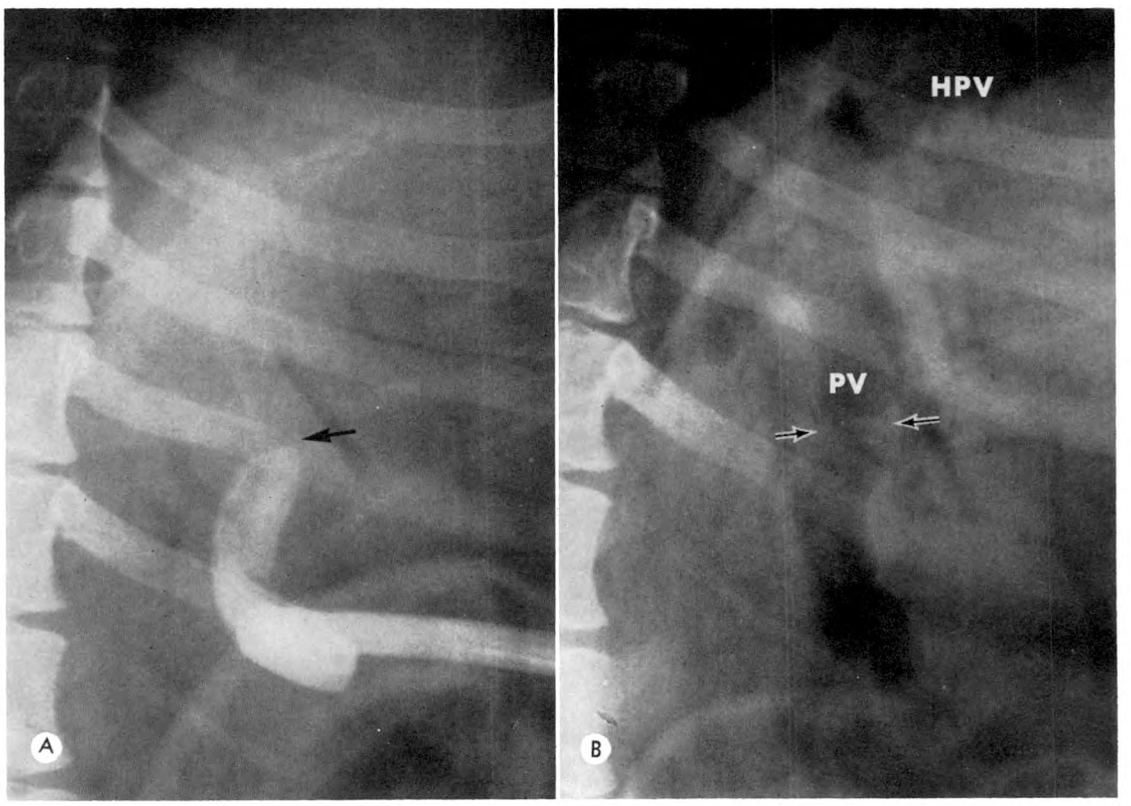


FIG. 2. *Partial obstruction.* Conventional study (*A*) shows radiopaque contrast only up to the site of ligature. (*B*) Capnosplenoportography demonstrates the site of obstruction (arrow) and the entire splenoportal venous system.

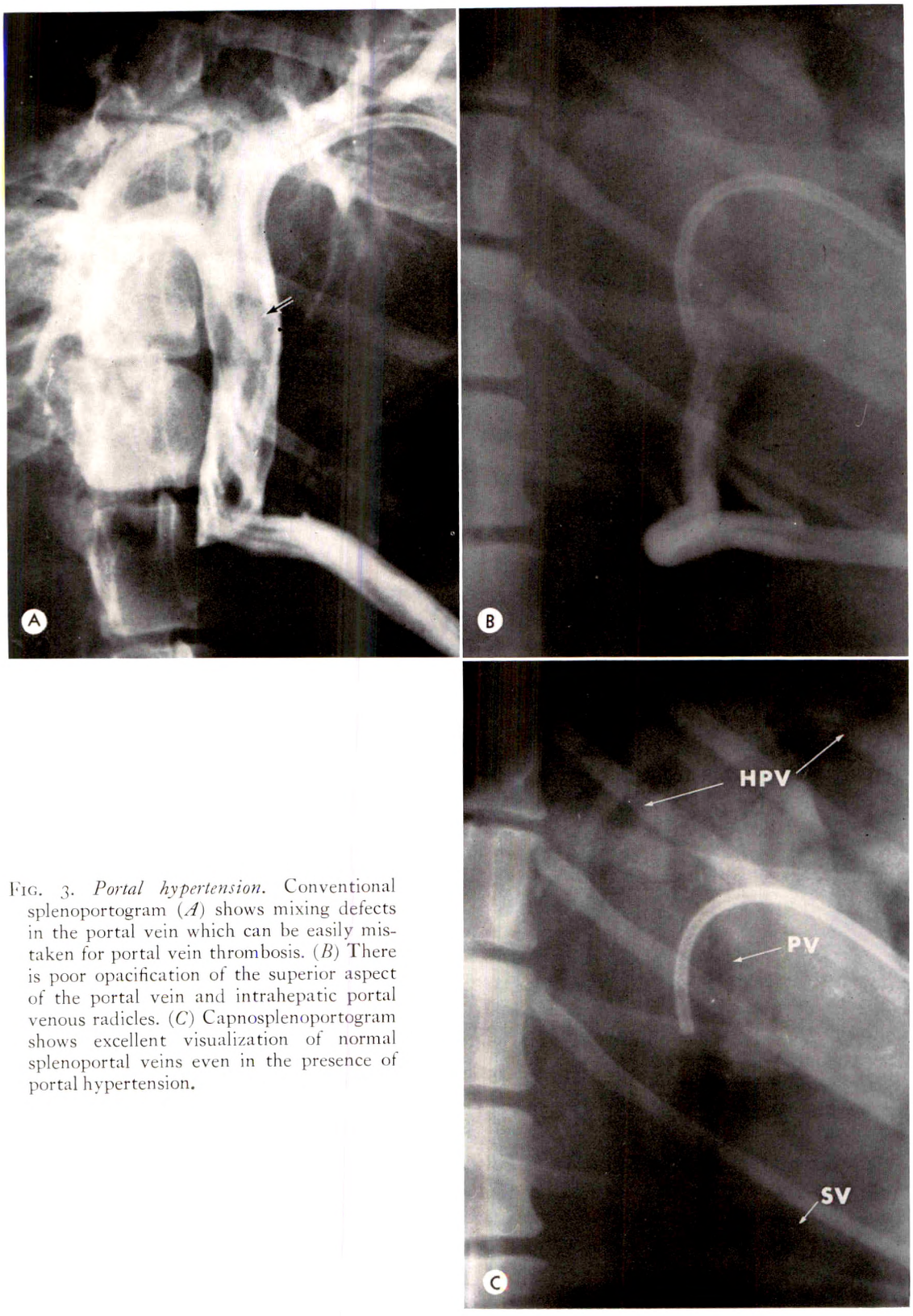


Fig. 3. *Portal hypertension.* Conventional splenoportogram (*A*) shows mixing defects in the portal vein which can be easily mistaken for portal vein thrombosis. (*B*) There is poor opacification of the superior aspect of the portal vein and intrahepatic portal venous radicles. (*C*) Capnosplenoportogram shows excellent visualization of normal splenoportal veins even in the presence of portal hypertension.

examinations.[1,7,8,9] Negative contrast techniques have recently been used in many intravascular examinations.[2,4,6,10,11,12,14,17] The gas usually employed is carbon dioxide because it is relatively innocuous and easily diffuses into the blood stream.[3,6,11,14] It has been utilized in visualizing the hepatic veins of the right lobe of the liver (capnohepatography).[2]

This proposed technique of negative contrast splenoportography is a guided regulated use of carbon dioxide gas in the portal venous system. The examination can be performed in the supine anteroposterior position as is usually done for the standard splenoportography. The ideal position is the left lateral decubitus or the left posterior oblique. The latter projection is preferred to avoid superimposition of the portal vein on the lumbar spine. The liver is higher than the spleen in these positions, due to the physical property of buoyancy of gas in a liquid environment.

The examination is feasible and outlines the splenoportal venous system. The findings in the normal dog using negative contrast study are similar to those of the positive contrast examination. In the presence of portal vein occlusion and simulated portal hypertension, the splenoportographic study with iodinated contrast media shows the portal vein inconsistently or not at all.[1,7,8,13] Contrast material entering the portal vein is diluted and held up by obstruction or hypertension resulting in poor visualization of the portal vein. The major volume of contrast material stagnates in the major channels and opacifies the collateral veins. When carbon dioxide is used, the proximal and distal aspects of the ligature can be readily outlined as well as the collateral venous pathway. It also determines the patency of the portal vein in portal hypertension.

Our investigations under induced pathologic conditions indicate that the duration of splenoportographic examination with iodinated contrast material should be prolonged in order to visualize the delayed circulation, site of pathology and collateral circulation. With the use of carbon dioxide, there is no need to prolong the duration of examination. The optimum time of visualization of the abnormal portal vein is essentially similar to that of the normal portal vein experimentally.

POSSIBLE CLINICAL APPLICATIONS

Experimental evidence favors the study in both normal and induced pathologic conditions. The examination has yet to be performed in the human, but gas has been seen in the portal vein in ischemic necrosis of the small bowel.[15,16]

1. The study appears to be most applicable in those cases with portal hypertension where there is nonvisualization of the portal vein by the usual type of splenoportography. With the injection of carbon dioxide gas through the same needle used for regular splenoportography, patency or thrombosis of the portal vein can be determined immediately. Thus, a surgical exploration or another study is avoided.

2. Carbon dioxide gas may be used as a radionegative contrast agent in splenoportography of patients with hypersensitivity to iodinated contrast material.

It has been suggested that carbon dioxide should not be used in patients with emphysema and other respiratory abnormalities.[13] The intravascular administration of this gas under these conditions may provoke an acute respiratory and systemic collapse.

SUMMARY

The use of carbon dioxide gas as a radionegative contrast agent in splenoportography under experimental conditions is reported.

The portal venous system in dogs was studied in the normal, after partial and complete occlusion of the portal vein, and in simulated portal hypertension. Comparative serial roentgenograms were made employing 60 per cent methylglucamine diatrizoate and carbon dioxide gas.

Splenoportography with carbon dioxide gas demonstrates partial or complete oc-

clusions of the portal vein either directly or via collateral vessels. Similar results are not reproduced consistently using conventional positive contrast agents when the blood flow is mainly hepatofugal.

In artificially induced portal venous hypertension carbon dioxide splenoportography demonstrates very well the patency of the portal vein. Using 60 per cent methylglucamine diatrizoate, there is poor visualization of the portal vein due to a mixing defect (streaming), dilution of contrast material and prolonged transit time in the portal vein.

The ideal position is a left posterior oblique projection. The duration of examination in the normal is 10 seconds, optimal demonstration of the portal vein occurring 2–4 seconds from the start of injection. This does not appreciably change even under induced experimental pathology. A dose of 2–3 cc./kg. carbon dioxide gas is adequate for good visualization of the splenoportal venous system.

Capnosplenoportography is a feasible examination in the experimental animal. It has clinical applicability in patients who are hypersensitive to iodinated contrast media and in instances where there is nonvisualization of the portal vein by conventional splenoportography.

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SPLENIC PULP PRESSURE: THE EFFECT OF INJECTION OF CONTRAST MATERIAL DURING SPLENOPORTOGRAPHY*

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DURING the performance of percutaneous splenoportography, we noted a striking elevation of splenic pulp pressure following the injection of the contrast material. Since we were not previously aware of the phenomenon, the pulp pressure was measured in subsequent studies before and after the injection of contrast material, with similar results. This report is a presentation of the results of our study, which we believe to be of clinical significance.

HISTORICAL BACKGROUND

Percutaneous splenoportography for many years has been recognized as a safe and valuable diagnostic method in the evaluation of the portal venous system and, in particular, in the evaluation of portal hypertension. The percutaneous method was used as early as 1949,[3] but the first report in the literature appeared in 1952.[9] Shortly thereafter, splenic pulp pressures were measured percutaneously and have proven to correlate well with portal venous pressure.[2,11,15,19]

METHODS AND MATERIALS

Splenoportography was carried out on 6 patients with splenic pulp pressures measured prior to and following the injection of contrast material. The classic percutaneous catheter technique, first mentioned by Fernstrom[12] and later described by Seldinger,[20] was utilized in all cases. The splenic pulp pressure was measured prior to injection of 40 cc. of 60 per cent methylglucamine diatrizoate (renografin) either with a water manometer or with a Statham transducer and Sanborn recorder. When the water manometer was used, it was filled with saline which was allowed to flow into the spleen. The pressure was then recorded when the saline column stabilized. In all of the measurements, the zero pressure level was 10 cm. above the table. Free flow of venous blood was taken as an indication that the catheter tip was correctly located in the splenic pulp. The correct position was confirmed in all cases with test injections of contrast material and subsequent splenoportogram. In none of the cases was there a significant extravasation of contrast medium into the peritoneal cavity. All of the injections were performed with a pressure injector at 75 pounds per square inch. The splenic pulp pressure was measured again immediately following the injection of contrast material in all cases, and also 10 minutes after the injection in 4 of the cases. In the last case, the pressure was monitored continuously before and after the injection.

RESULTS

The splenic pulp pressures recorded prior to and after injection of the contrast material are listed in Table 1. The maximum pressure recordable with the manometer was 650 mm. of water. In each patient, there was a pressure increase of at least 110 mm. of water immediately following injection except in the first patient, in whom the pressure was too high to be measured. In the last 4 patients, in whom pressures were measured 10 minutes after injection, the pressure elevation was demonstrated to persist. In some cases, the pressure had increased at 10 minutes above that level measured immediately after injection. In the last patient, the splenic pulp pressure returned to approximately the preinjection values at 15 minutes after injection (Fig. 1).

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TABLE I

SPLENIC PULP PRESSURES

Case No.	Pressure Prior to Injection (mm. H_2O)	Pressure Post Injection (mm. H_2O)	Pressure 10 Minutes Post Injection (mm. H_2O)	Diagnosis
1	590	>650		Portal vein thrombosis
2	300	500		Laennec's cirrhosis with varices
3	375	535	650	Laennec's cirrhosis with varices
4	280	480	500	Mild cirrhosis with normal splenoportogram
5	500	610	650	Laennec's cirrhosis with varices
6	130	270	250	Carcinoma of esophagus with normal splenoportogram

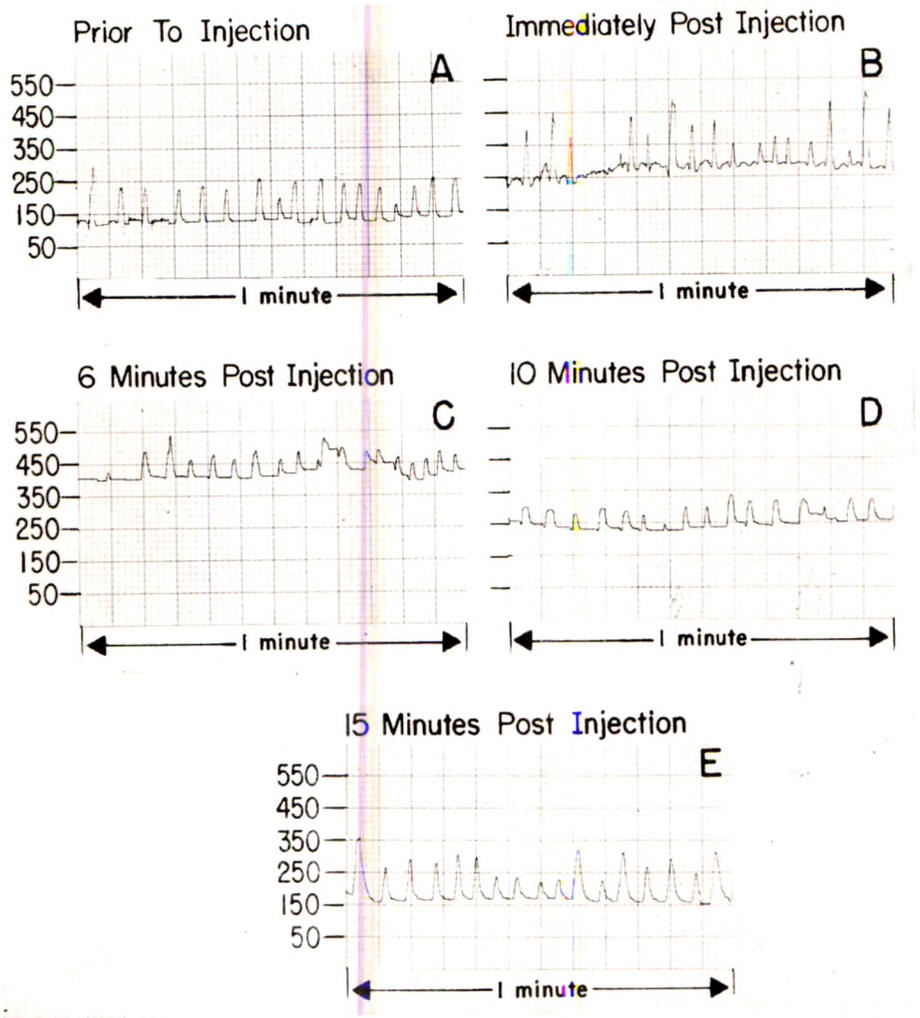


FIG. 1. Excerpts from a continuous recording of the splenic pulp pressure before and after injection of 40 cc. of 60 per cent methylglucamine diatrizoate in Case 6.

DISCUSSION

Most of the reports reviewed in the literature fail to mention the effect of contrast material on splenic pulp pressures. Leger[16,17] refers to artificial elevation of the splenic pulp pressure of 15 to 20 mm. of water lasting to 30 seconds after injection. He quotes the article by Le Go,[18] who demonstrated this minimal transient increase in the pressure. Rousselot and Burchell[19] do not mention a change in the splenic pulp pressure following the injection of contrast material. Bergstrand and Ekman[4] apparently have not observed an artificial increase in the pressure, but they do refer to the previous articles by Leger and Le Go. Arner and Fernstrom[1] found the splenic pulp pressure to be widely variable and not a reliable index of portal pressure. They noted an increase in the splenic pulp pressure up to 4 cm. of water following the injection of contrast material in 3 cases where duplicate measurements were taken. Semin[21] measured pressures prior to and after the injection of contrast material and noted either an increase or decrease of 3 to 4 cm. of water following the injection. In the majority of cases, no significant pressure change occurred. De Smet and Lahon[7] performed 177 splenoportographies on 100 patients and measured the splenic pulp pressure prior to and after the injection of contrast material in each instance. They noted that in 90 per cent of the cases, "a strong contraction" was associated with an elevation of the splenic pulp pressure from 10 to 40 cm. water. This was noted immediately following the injection and frequently lasted more than 10 minutes. This is the only reference found describing pressure changes similar to those which we have observed.

There are a number of articles in the literature describing the effects of various drugs on the portal pressure. Dreyer[10] and also Bergstrand and Ekman[5] noted that the injection of saline into the spleen produced no change in the portal pressure in dogs. Several authors report that epinephrine and other sympathomimetic drugs injected into the portal or systemic veins produce an increase in portal pressure.[6,8,14,22]

Bergstrand and Ekman[5] noted that approximately 0.5 to 1 minute after every injection of contrast material into canine spleens, the portal pressure increased 2 to 4 cm. of water.

Arner and Fernstrom[1] found the splenic pulp pressure to be quite variable in normal patients. They noted the intrasplenic pressure to be as high as 70 cm. of water in 2 to 18 normal control patients. They also noted wide variations in pressure depending upon the needle position in the spleen. In a few cases, the needle was either in the splenic artery or splenic vein, which explains some of the abnormal pressure values. They measured the splenic pulp pressures either before or after the injection of contrast material, but do not state whether those cases with abnormally high pressures were measured before or after the injection.

The reference point for zero pressure in recording the splenic pulp pressure is quite variable in the literature. We have chosen zero to be 10 cm. above the table top in this series. In any event, the importance of these values lies in the relative pressure before and after injection rather than in absolute pressures. It should also be noted that, as the catheter was removed from the splenic pulp in the last 3 cases, continuous pressure readings were obtained and the pressures did not change more than 3 cm. of water. In none of these cases did the splenoportogram suggest that the catheter tip was in an artery or directly in the splenic vein.

The importance of measuring the splenic pulp pressure prior to injection of contrast medium was well illustrated in the last case where the splenic pulp pressure, prior to injection, was within normal limits and where the splenoportogram was normal. If the pressure had been taken after the injection of contrast material, the value would have been in the range where many investigators would consider it abnormal.

We have not attempted to investigate the mechanism by which contrast material causes an artificial elevation of splenic pulp pressure. Several mechanisms seem plausible, such as increased resistance to blood flow in the liver or secondary splenic or venous contraction.

CONCLUSIONS

In 6 patients, the splenic pulp pressure was measured prior to and after the injection of contrast material. In each case, there was an artificial elevation of the pressure up to 275 mm. water lasting more than 10 minutes after the injection. This elevation of pressure may be sufficient to cause an erroneous diagnosis of portal hypertension if the pressure is not measured prior to the injection. Therefore, splenic pulp pressure should always be measured prior to the injection of the contrast material.

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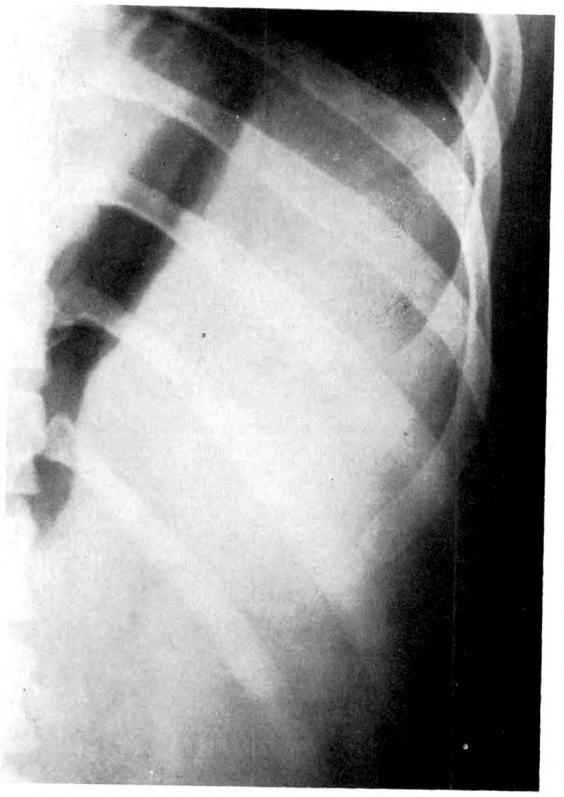


FIG. 4. Case 1. Left upper quadrant in supine position. Medial displacement of the air-filled stomach.

stomach and left abdominal wall was markedly increased with a local concavity on the greater curvature of the stomach. Following this examination, laparotomy was performed and black blood clots were found in the peritoneal cavity from the lacerated spleen.



FIG. 6. Case II. Left decubitus roentgenogram. Note the concavity at the cardiac portion of the stomach and increased gastroparietal distance. Splenic rupture was found at operation.

Comment. This was the first patient on whom we used the left decubitus procedure. Although the diagnosis was obvious in the plain abdominal roentgenogram, this case served to prove the validity and reliability of the procedure and sign.

CASE II. G.M., a 19 year old male, was hit by a car on his left chest and abdomen. He complained of "severe pain in the chest and all over the belly." Muscular rigidity and rebound tenderness in the upper part of the abdomen were found. An acute abdomen was suspected. The plain roentgenograms of the abdomen in the supine and erect positions did not reveal signs of acute abdomen. The gastric air bubble was displaced medially, but no definite diagnosis of splenic rupture could be made. The left decubitus roentgenogram of the barium-filled

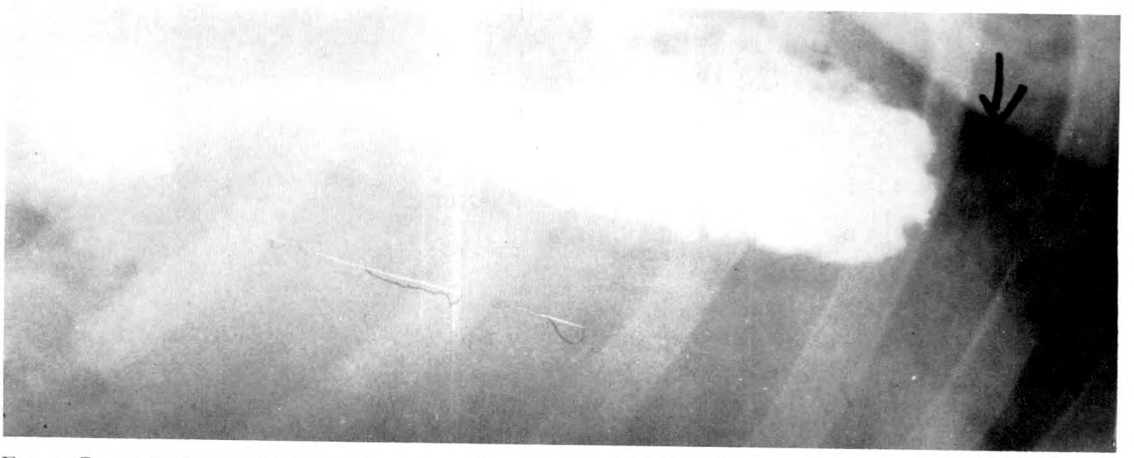


FIG. 5. Case 1. Left decubitus roentgenogram. The local concavity at the greater curvature and the increased distance from abdominal wall are evident. Splenic rupture was found at operation.

stomach (Fig. 6) showed deviation of the greater curvature medially and upwards, especially in the fundus region. This led us to suspect splenic rupture. On operation, over a liter of blood was found in the peritoneal cavity. The spleen was ruptured and bleeding. Many blood clots were found between the spleen and the diaphragm, together with edema and hemorrhage in the tail of the pancreas.

Comment. Here, the left decubitus examination led to the definite diagnosis of splenic rupture, in a case where the surgeons could not make more than a general diagnosis of acute abdomen.

Case III. B.S., a 63 year old female, fell and hit her elbow against her left flank. Four hours after the accident, symptoms of shock supervened and she was referred to our hospital. On admission, the patient was pale, blood pressure was 60/40 mm. Hg and the pulse was rapid and filiform. The patient complained mainly of pain in the left shoulder, especially during deep inspiration. The roentgenograms of the chest as well as of the left shoulder were negative. Plain roentgenograms of the barium-filled stomach, in the supine position, showed the cardia and body of the stomach displaced over the spine; the splenic flexure of the colon was filled with a large amount of gas and interposed between the stomach and the abdominal wall (Fig. 7). Since it was not clear if the medial shift of the stomach was due to the interference of the gas-filled splenic flexure of the colon or to an increase in the size of the spleen, a left decubitus roentgenogram was made. The distance between the greater curvature of the stomach and the abdominal wall was considerably increased, as was the distance between the gas-filled splenic flexure of the colon and the abdominal wall (Fig. 8), indicating that the shift was due to an enlarged splenic mass. On laparotomy, the spleen was found to be ruptured along its whole convex border, with large blood clots attached and a large amount of blood in the peritoneal cavity.

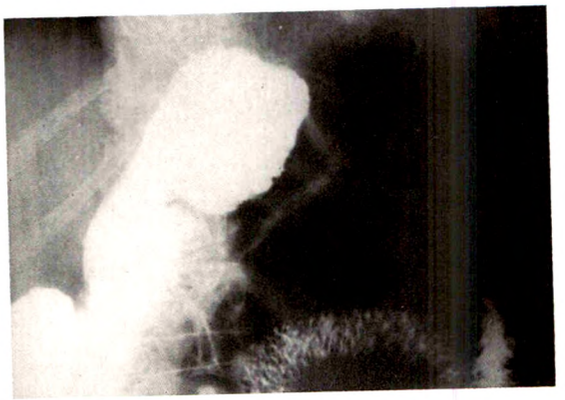


Fig. 7. Case III. Left upper quadrant roentgenogram in supine position of the barium-filled stomach. Medial displacement of the cardia and body of the stomach. Gas-filled splenic flexure.



Fig. 8. Case III. Left decubitus roentgenogram. Note the markedly increased gastroparietal distance. Splenic rupture was found at operation.

Comment. The surgeons were very reluctant to operate on this patient, because no definite signs of acute abdomen were present. The question as to whether the medial position of the stomach was due only to habitus and/or to displacement by the splenic flexure of the colon, or whether it was due to increased splenic mass, was resolved by the aid of the left decubitus roentgenogram.

Case IV. H.M., a 54 year old male, following a punch in the lower part of his left chest, was examined in the casualty ward. Since there were no particular findings, he was sent home. The next day he suddenly fainted and was readmitted to this hospital. Extreme tenderness of the left lower ribs was noticed. Blood pressure, as well as blood cell count were within normal limits. No clinical signs of acute abdomen were found. The patient was able to walk to the x-ray department. The chest roentgenogram showed a fracture of the 9th left rib. The plain roentgenogram of the left upper quadrant in the recumbent position demonstrated a slight medial shift of the splenic flexure of colon, which was interposed between the stomach and abdominal wall. No air was seen in the stomach. The left

decubitus roentgenogram (Fig. 9*A*) showed an increased distance between the greater curvature of the stomach and the abdominal wall. Because of the patient's good clinical condition, the surgeon was not convinced by the roentgenologic evidence of splenic rupture. On follow-up, 4 days later, the left decubitus roentgenogram of the left upper quadrant showed that the distance between the greater curvature of the stomach and the left abdominal wall had increased (Fig. 9*B*). This finding was consistent with the assumption that the spleen had been ruptured and that there was continued bleeding. On laparotomy, about 2 liters of blood with clots were present in the peritoneal cavity. The omentum, colon and stomach were adherent to the spleen, which was found to be ruptured into many pieces.

Comment. This case exemplifies how mild the signs and symptoms may be even in a major injury of the spleen. It is to be stressed that no air was present in the stomach, although an air-filled stomach is a common finding in such cases. The left decubitus roentgenogram helped to eliminate the interference of the colon. The repetition of the roentgen examination made the diagnosis clearer.

CASE V. S.E., a 40 year old male, was hit on the left lower part of his chest. On the next day pain began in his left lower chest and left hypochondrium The upper part of the abdomen was somewhat tender and distended. Muscular rigidity in the left hypochondrium was found.

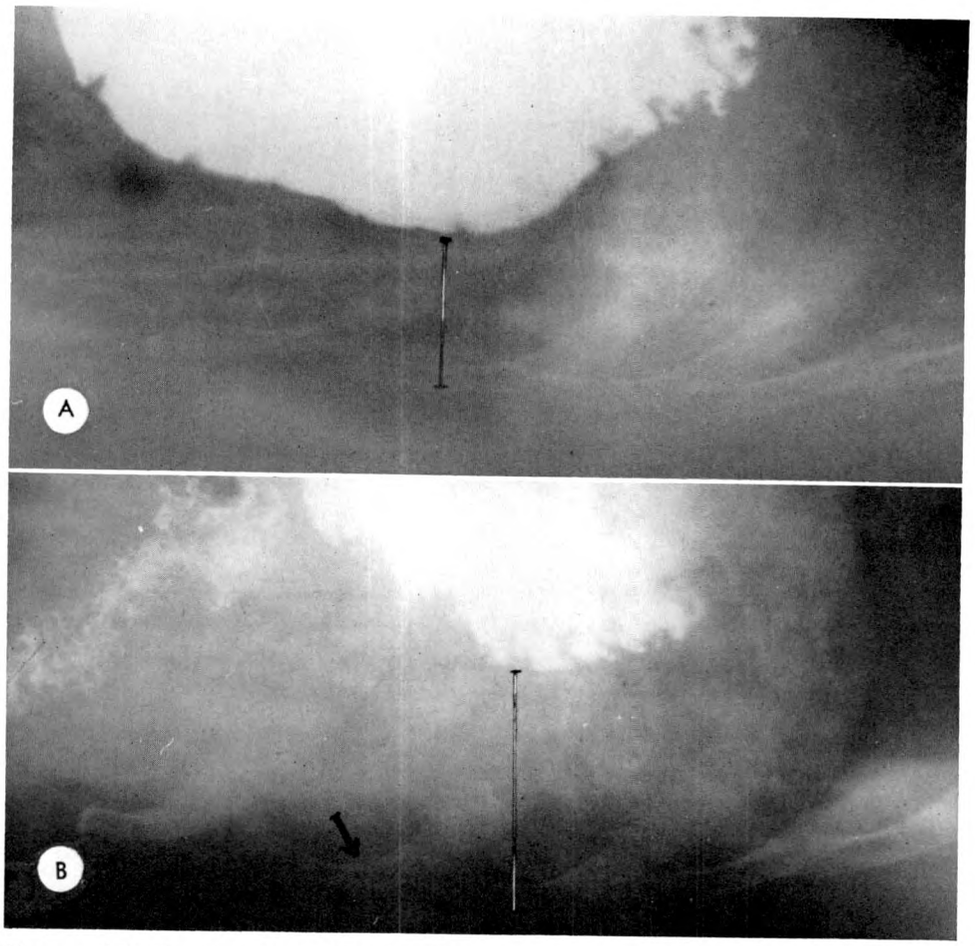


FIG. 9. Case IV. (*A*) March 12, 1964. Left decubitus roentgenogram. Moderately increased gastroparietal distance. (*B*) March 16, 1964. The distance between the stomach and abdominal wall is markedly increased. (Small difference in quantity of the barium swallowed is not of major importance.) Splenic rupture was found at operation.

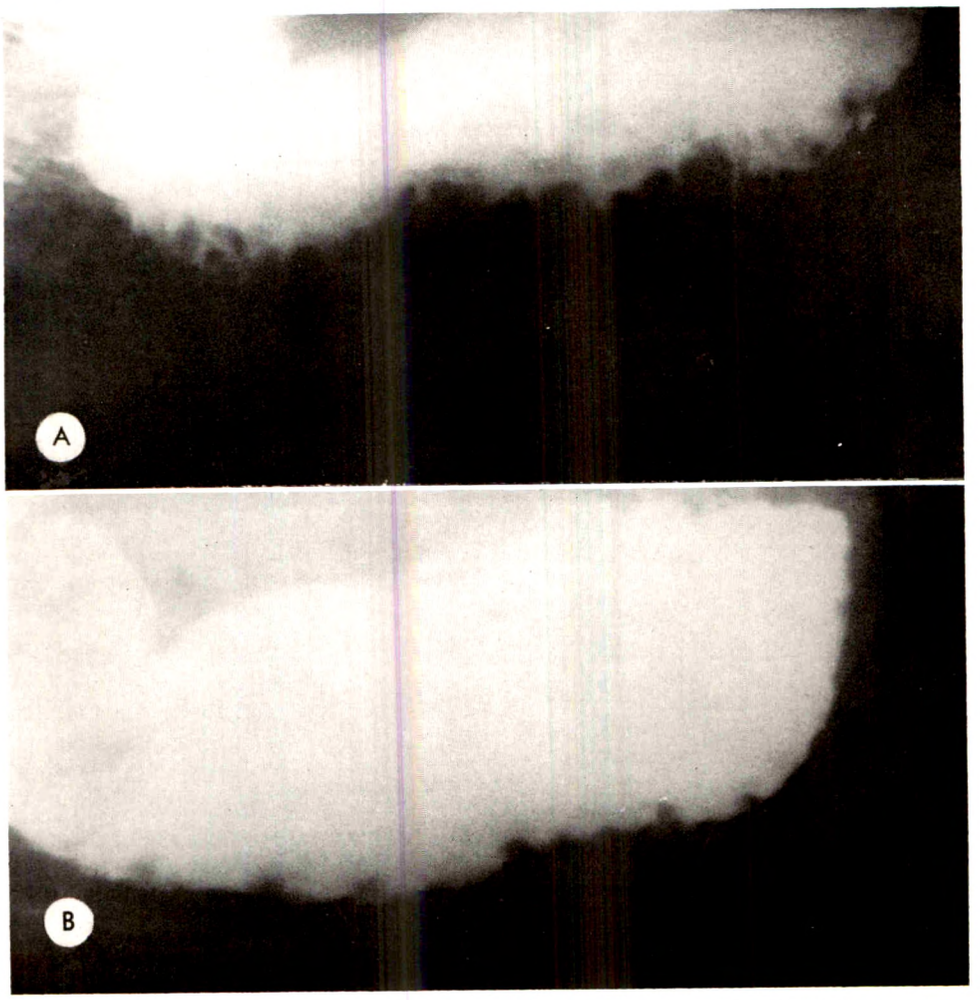


Fig. 10. Case v. (*A*) April 11, 1964. Left decubitus roentgenogram. The gastroparietal distance is markedly increased, accompanied by a slight local concavity. (*B*) April 19, 1964. The gastroparietal distance is now within normal limits. Probably an occult splenic rupture mass was present and reabsorbed; no operation was performed.

The plain roentgenogram of the left lower chest and left hypochondrium revealed an obliterated left costodiaphragmatic sinus. There was no rib fracture. Since a splenic rupture was suspected clinically, a left decubitus roentgenogram of the barium-filled stomach was made. The distance between the greater curvature of the stomach and abdominal wall was 7 cm. (Fig. 10*A*). A roentgen diagnosis of splenic rupture was made. Because his general condition was good, the surgeons thought that a laparotomy was not indicated. However, the patient was kept under meticulous observation and after 8 days when he was almost free of symptoms, a control left decubitus roentgenogram was made. At this time, the distance between the stomach and abdominal wall was within normal limits (Fig. 10*B*).

Comment. On the first left decubitus roentgenogram, the distance between the stomach and the abdominal wall was increased, but on the later examination this distance was normal. Although we have no definite operative proof, it is likely that a subcapsular splenic hemorrhage had occurred and was later absorbed.

Case vi. A 9 year old boy was brought to the hospital after a car accident. A fracture of the humerus was found. The patient was pale, hemoglobin was 9 gm. per cent, the pulse rate

was 116 per minute, blood pressure 110/80 mm. Hg, and there was tenderness of the whole upper part of the abdomen. All these findings aroused suspicion of splenic rupture. A plain roentgenogram of the abdomen did not reveal free air. The left decubitus roentgenogram after a barium meal showed a normal distance between the greater curvature of the stomach and the lateral abdominal wall, which was not consistent with the diagnosis of splenic rupture. Nevertheless, because the clinical picture was that of intra-abdominal hemorrhage, a laparotomy was performed revealing a rupture of the right lobe of the liver with a large amount of blood in the peritoneal cavity.

Comment. In this case the clinical picture was strongly suggestive of ruptured spleen, but as the finding on the left decubitus roentgenogram was negative we could exclude this diagnosis. On laparotomy, a ruptured liver was found to be the cause of the intraperitoneal bleeding, while the spleen was intact.

DISCUSSION

The spleen is free in its lateral, cranial and caudal margins, and, therefore, not strongly fixed in its position in the left upper hypochondrium. The spleen may lie in a horizontal position underneath the left diaphragmatic dome or in a vertical craniocaudal position. It is in close contact with the stomach through the gastrosplenic ligament. Posterolaterally, it is wedged between the diaphragm and the stomach.

The relationship of the upper part of the stomach to the spleen is sufficiently constant under normal conditions, to serve as a landmark of considerable reliability.[4,6] In the left decubitus position, the barium-filled stomach falls by gravity to its lowest possible limit and impinges upon the normal or the injured spleen. The roentgen sign described above is based on the relative mobility of the spleen and its proximity to the greater curvature of the stomach. Encroachment of the enlarged mass of the spleen on the adjacent organs is one of the main signs of splenic rupture, but the frequent interposition of the small intestine and the splenic flexure of the colon interferes with the anatomic relationship between the stomach and the spleen. Such interposition is the cause of major pitfalls in the diagnosis of enlarged splenic mass. The left decubitus position with barium-filled stomach obviates these difficulties.

The left decubitus procedure might serve as a baseline for serial follow-up examinations for several days or weeks, looking for signs of delayed hemorrhage from the spleen which may result from minimal capsular rupture, intrasplenic hematoma or perisplenic hematoma. The careful reexamination of patients showing nothing more definite than medial displacement of the cardia in the left decubitus position may often lead to recognition of splenic rupture. In a similar approach to this problem, Gershon-Cohen *et al.*[3] reported in 1951 an examination with barium-filled stomach of a patient in the Trendelenburg position. This maneuver, when repeated, may show progressive changes which are diagnostic of a bleeding spleen.

Until some specific means for more accurate roentgenologic diagnosis of splenic rupture is available, the roentgenologist can improve his diagnostic accuracy by adding the left decubitus procedure to other routine examinations. Though it cannot be considered as an infallible sign, the displacement of the gastric cardia and/or the body of the stomach overlying the injured spleen in the left decubitus position will often lead to clarification when the clinical and roentgenologic signs are ambiguous.

We have been using the left decubitus roentgenogram for the diagnosis of splenic rupture for about 2 years. During this period over 30 cases of injury in the left hypochondrium were examined by this maneuver, some of them with a strong clinical suspicion of splenic rupture. In most we could exclude splenic rupture by this roentgen procedure, and have saved some superfluous laparotomies. In 5 cases in which a roentgen diagnosis of splenic

rupture was made, the diagnosis was confirmed by the operative findings.

In 2 other patients we made a positive diagnosis of splenic rupture, but as their general condition was quite good the operation was postponed and they were kept under strict observation. In follow-up roentgenograms, the increase in the distance between the stomach and left abdominal wall disappeared. This was in accordance with the clinical improvement. We assume that these 2 patients had splenic hematomata which remained subcapsular and were later absorbed. The medical literature hardly mentions this kind of subcapsular splenic bleeding which regresses and absorbs spontaneously. This is probably due to the fact that often splenic hematomata do not give clear-cut clinical and roentgenologic signs until they rupture.[1,2] Thus, it is not surprising that splenectomy is considered to be the only treatment for an injured spleen. Most probably the milder cases of splenic rupture with spontaneous cure are not recognized. Lorimer[5] says on this: " . . . There are a certain number of patients who survive major rupture of the spleen undiagnosed and untreated. They have an entity which will be referred to as occult rupture of the spleen." Because the procedure described here is more sensitive than the conventional examination, we believe we have been able to diagnose 2 cases of occult splenic rupture that were spontaneously cured. The whole entity of occult and reversible splenic rupture deserves further study.

One of the greatest difficulties inherent in the left decubitus procedure is the differentiation between increased splenic mass due to rupture of hematoma and splenomegaly of other origin. This differentiation was usually achieved by means of the left decubitus roentgenogram (Fig. 2). While medial shift of the cardia is quite typical of splenic rupture, in cases of nontraumatic splenomegaly usually the more distal parts of the stomach are shifted medially, or there is a peculiar local concavity in the middle of the greater curvature. However, in some cases where there are difficulties in the differential diagnosis, the history and clinical findings as well as the roentgenologic follow-up make the diagnosis clear.

An additional use of the left decubitus procedure could be in cases in which an unidentified mass is palpated in the left upper quadrant; often this simple examination can show whether it is the spleen or not. This simple diagnostic procedure might be useful in following up changes in the size of the spleen after radiologic or chemotherapeutic treatment in cases of malignancies, such as lymphomata or leukemias.

This communication should be considered a preliminary one. Further study and widespread use of the left decubitus procedure are needed in order to come to more definite conclusions as to its value, reliability and disadvantages.

SUMMARY

Splenic rupture is a grave clinical condition which demands prompt treatment. Since the clinical and roentgenologic diagnosis of this entity is often inaccurate, we have described a new procedure consisting of an anteroposterior roentgenogram of the stomach after a barium meal, with the aid of a horizontal roentgen-ray beam, with the patient lying on his left side, referred to as "the left decubitus roentgenogram." In cases of splenic rupture, the distance between the greater curvature of the stomach, especially in the cardiac region and the abdominal wall, is increased.

Over 30 patients were examined by this procedure. In 5 of them it helped us to diagnose splenic rupture, later proved by laparotomy. Two other cases we believe to be examples of subclinical occult splenic rupture, which spontaneously regressed.

The usefulness of the left decubitus procedure and its pitfalls are discussed, as is the differential diagnosis between splenic

rupture and splenomegaly. The conclusions drawn are provisional and more experience is needed to assess its value in diagnosis.

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Vol. 99, No. 3

HEPATIC PORTOGRAPHY BY DIRECT CATHETERIZATION OF THE PORTAL VEIN THROUGH THE ROUND LIGAMENT OF THE LIVER (LIGAMENTUM TERES)*

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ONE of the limiting factors in the study of the hepatosplanchnic hemodynamics in health and disease is the inaccessibility of the portal vein.

In 1959, Gonzales Carbalhaes[3] devised a method for direct catheterization of the left branch of the portal vein, at its origin from the main trunk, passing through the ligamentum teres. This technique has been recently revived by Juliani and his colleagues,[4] Roberti *et al.*[5] and Storti and his co-workers.[6]

In a preliminary communication,[4] the technique was described and the first roentgenograms obtained with the method were shown; in the present work more technical details about the procedure and additional roentgenograms are presented.

MATERIAL AND METHOD

Three subjects with a normal liver and 8 patients with well compensated liver cirrhosis were examined in a fasting state. In all of the cases of cirrhosis, the diagnosis was confirmed by liver biopsy. In 1 of them, the disease was associated with a primary tumor of the left lobe of the liver.

In 7 cases the procedure was carried out under local anesthesia (xylocaine 2 per cent); in 3 cases, general anesthesia of short duration was induced by using pentothal and halothane. A vertical incision, 3 to 4 cm. long, was made along the xiphoumbilical line in its inferior third to a point 2 cm. above the umbilicus; the cutaneous, and subcutaneous tissues and the aponeurosis of the rectus abdominis muscles were incised. The round ligament, often surrounded by adipose tissue, was then isolated in the preperitoneal region.

The ligament usually had the appearance of a cord, but sometimes it was flat, similar to a lamina, in which case, it usually thickened progressively and resembled a cord before entering the peritoneum.

Through a transverse incision, a flexible, blunt probe was introduced into the virtual lumen of the ligament which was kept well stretched in the direction of the liver. After 15 to 20 cm. the wall of the portal vein offered a strong resistance which had to be overcome with decision.

After withdrawing the probe, a tipped catheter of the ureteral type or a Cournand catheter (size No. 7 to 9) was introduced, allowing a free flow of blood from the portal vein.

Serial studies were then made after rapid manual injection of 20 ml. of hypaque 70 per cent. In order to visualize both lobes of the liver, the catheter had to be withdrawn from 1 to 2 cm. after being wedged.

The whole procedure lasted no more than 20 to 30 minutes, unless portal vein pressure and portal vein blood flow had to be measured and portal vein blood sampled.

RESULTS

The technique was successfully performed in 2 normal persons and 7 cases of cirrhosis with no complications being noted. In 1 normal case, the ligament had the appearance of a thin ribbon along its entire extraperitoneal length and the procedure was abandoned; in 1 case of cirrhosis the probe perforated the cord and entered the peritoneal cavity. In this patient the ligament was not kept well stretched and the probe opened a false pathway.

Figure 1, *A-H* shows different phases of

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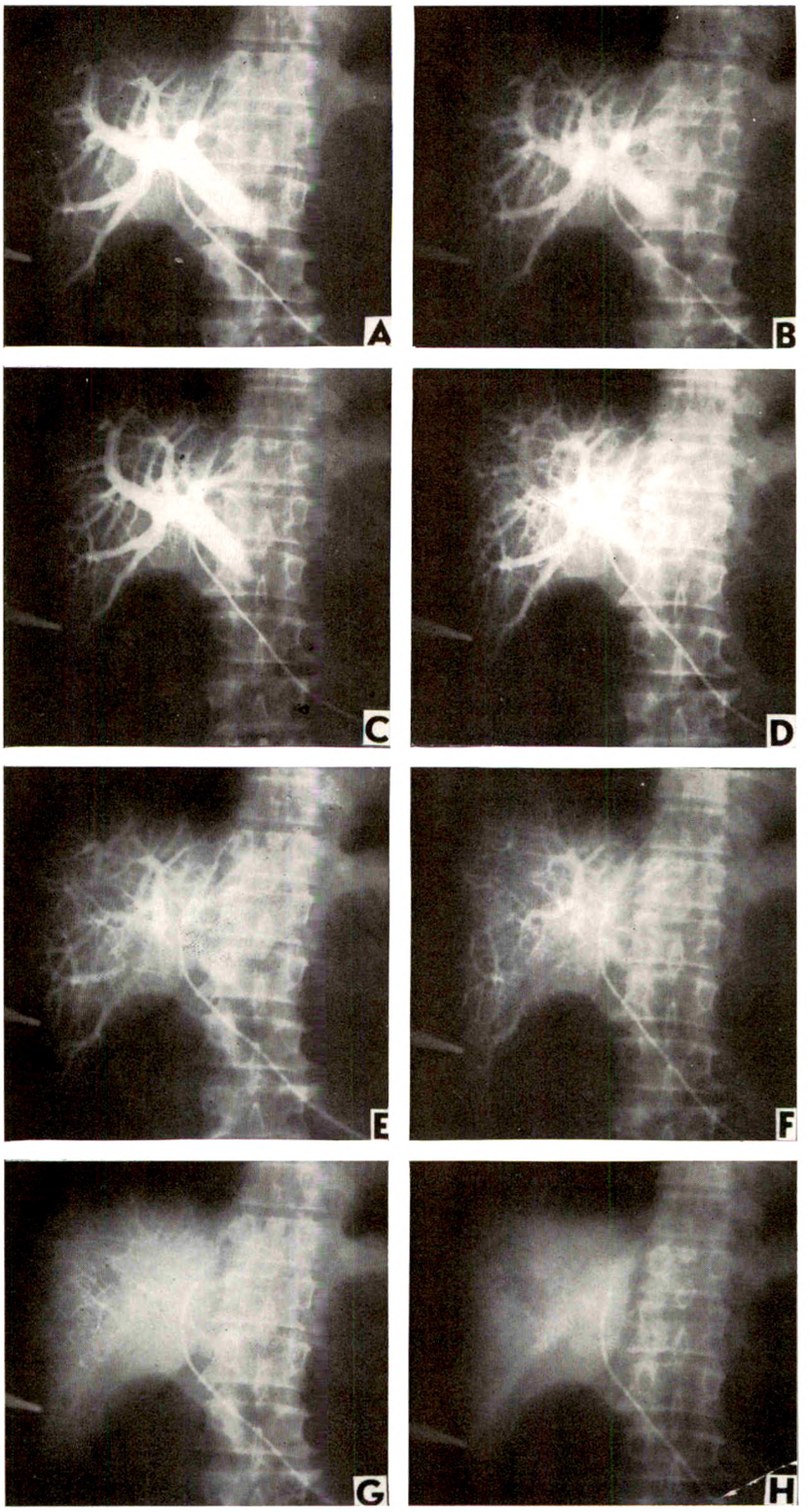


Fig. 1. Serial studies in a normal subject (*A*) 1 second; (*B*) 2 seconds; (*C*) 3 seconds; (*D*) 4 seconds; (*E*) 5 seconds; (*F*) 6 seconds; (*G*) 8 seconds; and (*H*) 10 seconds after the injection of 20 ml. of hypaque 70 per cent.

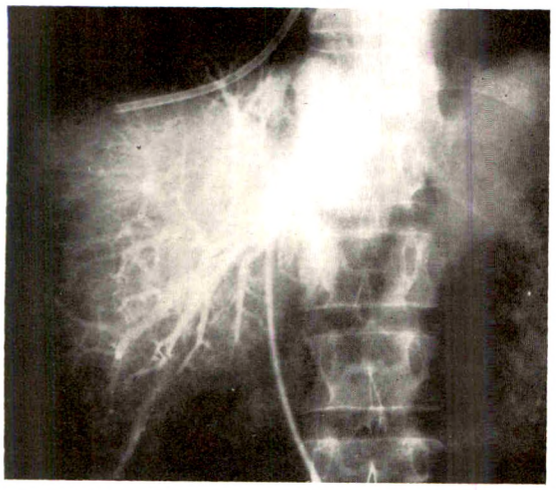


Fig. 2. Chronic active hepatitis. The intrahepatic portal branches are tortuous and stretched. A Cournand catheter is placed into a hepatic vein for the measurement of liver blood flow.

hepatic portography in a normal subject (rapid seriography). The intrahepatic portal branches are clearly visible in the seriograms made between 3 and 6 seconds following the injection. An excellent hepatographic effect, a true parenchymal opacification, appears evident between 10 and 12 seconds.

In patients with cirrhosis, the usual portographic appearance previously seen with splenoportography, was observed (Fig. 2).

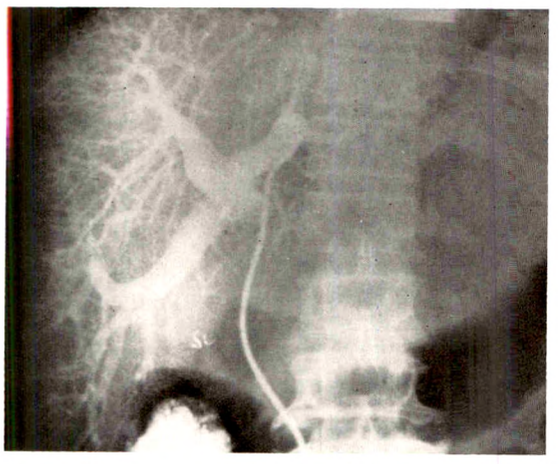


Fig. 3. Primary tumor of the left lobe of the liver in a patient with cirrhosis. There is amputation of some portal venules of the left branch of the portal vein.

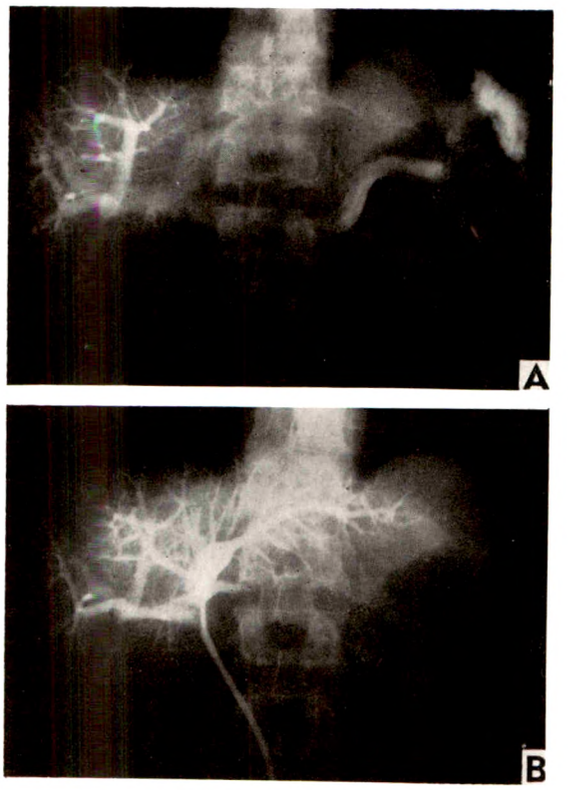


Fig. 4. (*A* and *B*) Studies showing a comparison between splenic portography and transumbilical portography in a subject with suspected metastases of the liver. In the splenic portogram, the left branch of the vena portae is poorly visualized.

Figure 3 shows a patient with cirrhosis and a primary tumor of the left lobe of the liver. The left branch of the portal vein seems to be almost completely obliterated and the portal vascularization of the left lobe is very poor.

Discussion and Conclusions

Direct catheterization of the portal vein represents an advance in the study of hepatosplanchnic hemodynamics. It allows: (1) direct measurement of the portal pressure; (2) the determination of portal vein blood flow separately from the flow of the hepatic artery;[1] (3) biochemical examinations of the portal blood (cathecolamines, serotonin, bradykinins);[2] and (4) direct portography.

The procedure, which appears to be safer than splenoportography, should be

the one of choice in patients with suspected portal hypertension and splenectomy, with thrombosis of the splenic vein, and with incomplete visualization of the portal intrahepatic vascular tree of the left lobe (Fig. 4, *A* and *B*). Finally, it should help in interpreting false images of thrombosis of the portal vein in patients with portal hypertension and large gastroesophageal collateral circulation. In these cases direct portography should prove useful in both diagnosis and therapy.

Furthermore, it should be emphasized that extremely clear visualization of the networks of the smallest intrahepatic branches of the portal vein and an excellent late hepatographic effect can be obtained with direct portography.

Direct portography has some disadvantages. It is more difficult than other procedures and, therefore, some failures occur. The splenic vein and the porto-systemic collaterals are not demonstrated and the main portal trunk is only partially visualized. However, in selected cases, its advantages outweigh its limitations.

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VOL. 99, NO. 3

SURVIVAL FOLLOWING ROENTGENOGRAPHIC DEMONSTRATION OF GAS IN THE HEPATIC PORTAL VENOUS SYSTEM

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GAS in the hepatic portal venous system was first described by Wolfe and Evans[7] in 1955. They reported 6 cases in which gas was noted ante mortem in infants who had a necrotizing enteritis associated with mesenteric artery thrombosis.

To date, this finding has been described in 18 patients, all of whom died shortly thereafter (Table I). It is the purpose of this communication to report a case of gas in the portal venous system associated with strangulated obstruction of the small intestine in which the patient survived.

REPORT OF A CASE

A 58 year old Caucasian woman was admitted with epigastric pain, nausea and vomiting for the previous 20 hours. This was followed by hematemesis and hematocolpia. The patient had 2 previous operations, a transabdominal uterine suspension 28 years ago and a vaginal hysterectomy 20 years ago.

TABLE I

CASES FROM THE LITERATURE DEMONSTRATING GAS IN THE HEPATIC PORTAL VENOUS SYSTEM

Authors	Symptoms at Age	Expired after Gas Seen	Premortem Diagnosis	Postmortem Findings			Postmortem Blood Culture
				Mechanical Bowel Obstruction	Mesenteric Artery Obstruction	Pneumatosis Intestinalis	
Wolf and Evans[7]	17 da.	15 hr.	imperforate anus	no	yes	jejunum, ileum colon	*E. coli*
	7 da.	7 da.	5 days postoperatively for duodenal atresia	jejunum	yes	no	*E. coli*
	14 da.	6 hr.	septicemia	no	yes	colon	*E. coli*
	16 da.	?	gastroenteritis	no	no	no	*E. coli*
	3 mo.	?	gastroenteritis	no	yes	duodenum, jejunum	*E. coli*
	18 da.	14 hr.	gastroenteritis	no	no	no	*E. coli*
Susman and Senturia[5]	70 yr.	20 hr.	mesenteric artery thrombosis	no	yes	no	not done
Sisk[4]	19 yr.	at surgery	hemorrhagic pancreatitis	no	no	stomach	not done
	81 yr.	7 da.	7 days postoperatively for mechanical ileal bowel obstruction,	no	yes	no	not done
	84 yr.	2 hr.	ileus and pneumonia	no	no	no	not done
Wiot and Felson[6]	63 yr.	?	5 days postoperatively for bowel resection for gangrenous ileum due to volvulus	no	yes	no	*Bact. aerogenes*
	35 yr.	8 hr.	diabetic coma	no	no	no	not done
	52 yr.	4 hr.	mesenteric artery thrombosis	no	yes	no	*Cl. parabotulinum* *Proteus mirabilis*
Barrett[1]	60 yr.	6 hr.	benign gastric ulcer	no	yes	no	*Cl. welchii*
	85 yr.	2 hr.	enterocolitis (necrotan)	no	no	no	*Cl. welchii*
Pagan-Carlo and DeMouy[3]	12 da.	48 hr.	gastroenteritis	no	yes	no	sterile
McCandless[2]	30 yr.	24 hr.	necrotizing colitis	no	no	colon	*Cl. perfringens* *E. coli*
	82 yr.	14 hr.	ischemia of the small bowel due to unknown causes	no	no	no	*Cl. perfringens* *E. coli* *Staphylococcus albus*

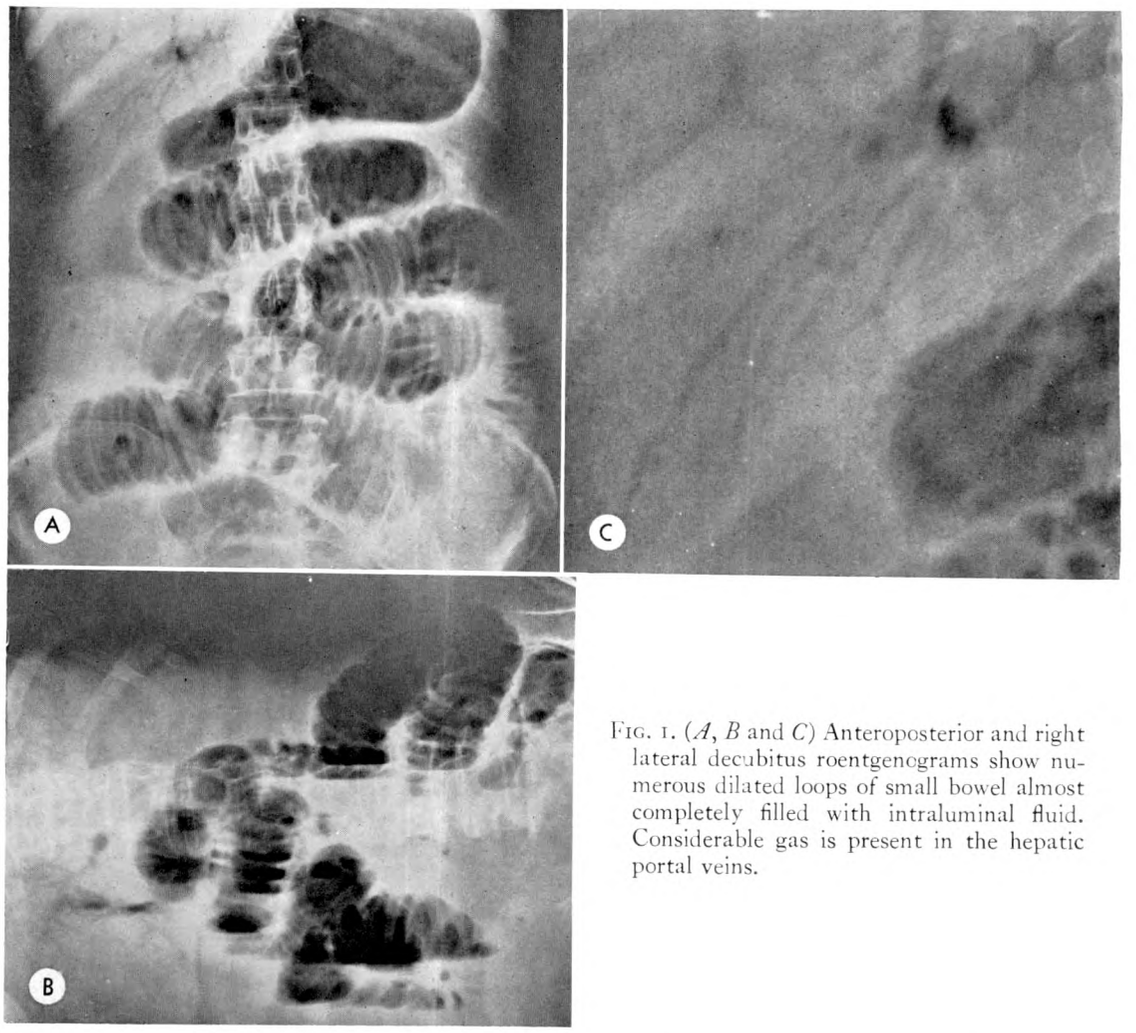


FIG. 1. (*A*, *B* and *C*) Anteroposterior and right lateral decubitus roentgenograms show numerous dilated loops of small bowel almost completely filled with intraluminal fluid. Considerable gas is present in the hepatic portal veins.

On examination, she was afebrile and in shock. Her abdomen was distended. The bowel sounds were normal and there was bright red blood found on rectal examination; also, bright red blood was aspirated from her stomach. Laboratory work showed a hematocrit of 29 per cent, hemoglobin of 17.2 gm. per cent, and a white blood cell count of 22,000. Urinalysis, serum electrolytes, blood urea nitrogen and serum amylase were normal.

The chest roentgenogram was normal. Anteroposterior and right lateral decubitus roentgenograms of the abdomen showed gastric dilatation and numerous dilated loops of small bowel almost completely filled with intraluminal fluid. Considerable gas was present in the hepatic portal veins (Fig. 1, *A*, *B* and *C*). There was no free intraperitoneal gas, pneumatosis cystoides intestinalis or ascites.

The patient was treated with intravenous fluids, plasma and blood preoperatively. At surgery, there was a band adhesion across the terminal ileum, producing an obstruction. The small intestine was gangrenous from 6 inches distal to the proximal jejunum to 2 inches proximal to the distal ileum. The involved small bowel was resected. The patient made an uneventful recovery. A roentgenogram made on the fourth postoperative day showed disappearance of the gas in the hepatic portal veins.

The pathologic specimen consisted of 125 cm. of grossly gangrenous small bowel. The lumen contained serosanguineous fluid. The mesentery was covered with fibrinous exudate and was filled with blood. Microscopic examination showed necrosis of the bowel wall. No thrombi were seen in the small arterials.

At follow-up clinic 1 month later, the patient

felt well, had not lost weight, and was having 1 to 2 normal stools a day.

DISCUSSION

Gas in the hepatic portal venous system appears to have 2 etiologies. In infants[3,7] and some adults,[1,3] there is an enterocolitis followed by sepsis and local necrosis of the bowel wall. The gases produced by necrosis are absorbed in the portal venous system and collect in the liver.

In most adults,[1,4,5,6] there is mechanical bowel obstruction or mesenteric artery thrombosis followed by vascular insufficiency and necrosis of the bowel wall. Necrosis is associated with gas production. If the portal venous system has remained patent, then the gases produced may be transported to the liver. Gas in the hepatic portal venous system is rarely seen in mechanical obstruction, probably because venous occlusion occurs early.

Gas in the portal venous system can usually be easily distinguished from gas in the biliary system and from hepatic or subdiaphragmatic abscesses.

SUMMARY

A case is reported in which gas was demonstrated in the hepatic portal venous system in a patient with gangrenous obstruction of the small bowel. Following surgical resection, the patient made an uneventful recovery.

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MAJOR ARTERIAL INVOLVEMENT BY PANCREATIC PSEUDOCYSTS

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PANCREATIC pseudocysts are loculations of fluid in the lesser peritoneal sac. They are thought to arise following activation of pancreatic enzymes with necrosis of pancreatic tissue, leading to rupture of the pancreas and internal drainage into the lesser peritoneal sac. Connection with the pancreatic duct is maintained. They are termed pseudocysts because they do not have an epithelial lining; instead, the wall is formed by peritoneum or adherent omentum. They are usually single and may attain a large size.[6]

The lesion is most often encountered in patients, generally alcoholics, with a history of repeated bouts of pancreatitis. They also occur in patients with biliary disease and in patients who have sustained blunt external abdominal trauma or abdominal surgery. Occasionally, cases occur without an obvious cause.[6,7]

In typical cases, the diagnosis is not difficult. The patient with recurrent pancreatitis who complains of upper abdominal and/or back pain and who presents with an upper abdominal mass is likely to have a pseudocyst.

Roentgenographically, depending upon the size and location of the pseudocyst, there is displacement of adjacent structures. Most commonly, there is displacement of the stomach anteriorly and to the left. There may be extrinsic pressure on the third part of the duodenum and downward displacement of the colon. There may or may not be calcification in the region of the pancreas.[6]

When the diagnosis of pancreatic pseudocyst is established, some form of surgical therapy is generally undertaken, in view of high mortality of cyst rupture and also because of possible pressure effects of the mass.[8]

Erb and Grimes[7] have reported an incidence of 38 per cent gross gastrointestinal bleeding in a series of 17 patients with pseudocysts. Most of their patients were anemic. The presence of other conditions in the gastrointestinal tract which would predispose to bleeding was not noted.

Several other authors have reported the occurrence of major vascular involvement by pseudocysts detected at the time of surgery or autopsy. Incorporation of the celiac vessels in the walls of a pseudocyst has been described by Byrd *et al.*,[3] and Doubilet and Mulholland[5] have reported a case in which there was brisk arterial bleeding following the opening of a cyst which incorporated the superior mesenteric artery. Carter and Slattery[4] reported a case in which brisk arterial bleeding was controlled by ligation of a large vessel entering the posterior surface of a cyst wall. In a number of other reported cases, there has been serious bleeding after surgery. Hillis[8] has reported a case of fatal hemorrhage caused by erosion of the splenic artery occurring 4 weeks following internal drainage of a pancreatic pseudocyst.

A bruit heard over an upper abdominal mass has recently been described in 2 patients by Bucknam.[2] Each of these patients had a history of alcoholism and a history compatible with chronic pancreatitis. In the first case, on exploration, a pulsating cystic structure in the lesser sac, measuring 15×25 cm., was found displacing the stomach and duodenum anteriorly and to the left. Needle aspiration and incision into the cyst showed that it was filled with bright red blood and old clots. The bleeding

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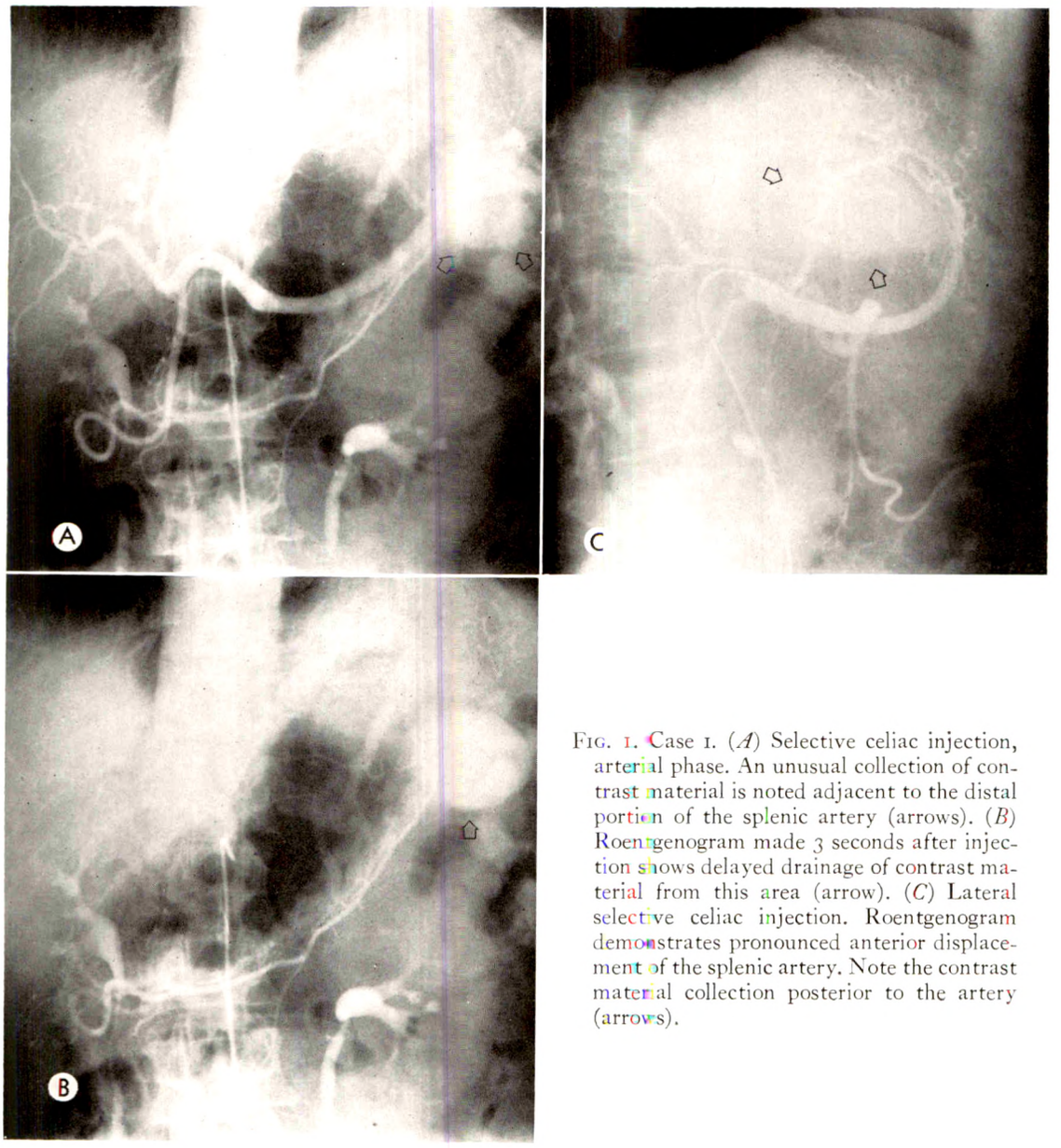


Fig. 1. Case 1. (*A*) Selective celiac injection, arterial phase. An unusual collection of contrast material is noted adjacent to the distal portion of the splenic artery (arrows). (*B*) Roentgenogram made 3 seconds after injection shows delayed drainage of contrast material from this area (arrow). (*C*) Lateral selective celiac injection. Roentgenogram demonstrates pronounced anterior displacement of the splenic artery. Note the contrast material collection posterior to the artery (arrows).

site was identified as the gastroduodenal artery. This was ligated. In the second case, a pulsatile, blood-filled mass was encountered in the region of the head of the pancreas. Active bleeding from the splenic artery in the posterior portion of the cyst wall was controlled. That vascular erosion is not confined to arteries is established in the report by Zeller and Hetz[12] of erosion of the portal vein by a pancreatic pseudocys This resulted in a fatal generalized fat necrosis.

We have recently had the opportunity to perform celiac angiography in 2 patients in whom pancreatic pseudocysts were suspected. In each case, there was an upper abdominal bruit and arteriography was done to determine if significant vascular lesions could be detected preoperatively.

The technique of performing celiac axis

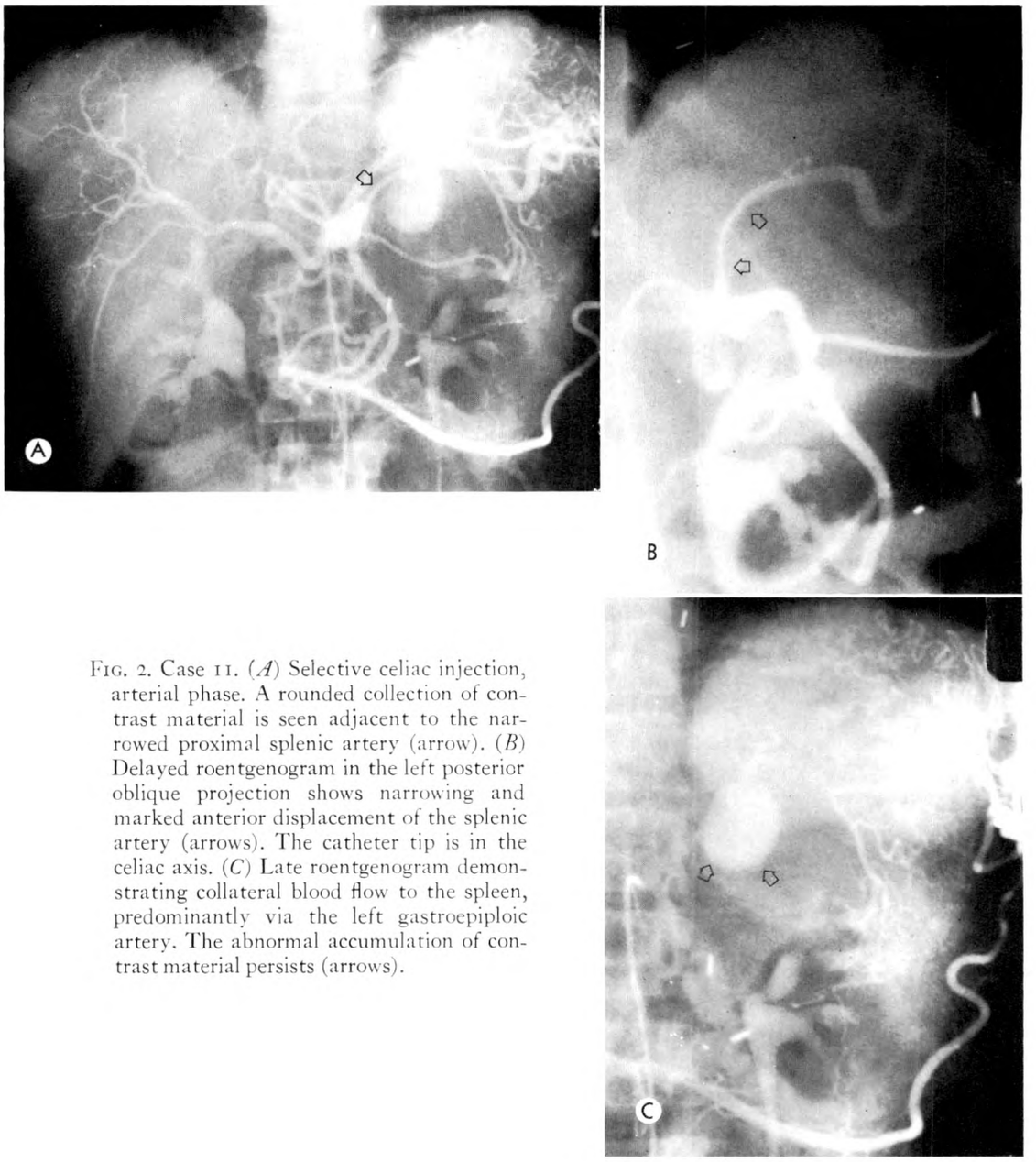


FIG. 2. Case 11. (*A*) Selective celiac injection, arterial phase. A rounded collection of contrast material is seen adjacent to the narrowed proximal splenic artery (arrow). (*B*) Delayed roentgenogram in the left posterior oblique projection shows narrowing and marked anterior displacement of the splenic artery (arrows). The catheter tip is in the celiac axis. (*C*) Late roentgenogram demonstrating collateral blood flow to the spleen, predominantly via the left gastroepiploic artery. The abnormal accumulation of contrast material persists (arrows).

angiography has been described previously.[9] Rösch and Bret[10] reported arteriographic abnormalities in 8 patients with pancreatic pseudocysts. These findings consisted principally of pressure changes on surrounding vessels. Baum *et al.*[1] describe rupture of a splenic artery aneurysm in a patient with the clinical picture of hemorrhagic pancreatitis which was diagnosed by celiac arteriography.

Arterial erosive changes in pancreatic pseudocysts can be diagnosed preoperatively by means of selective celiac axis angiography.

REPORT OF CASES

CASE 1. G.K., a 45 year old white male, was admitted to the hospital complaining of recent weight loss, weakness, postprandial epigastric pain and hemoptysis. The patient, who had

formerly been a heavy drinker, had had a perforated duodenal ulcer 5 years before. Physical examination disclosed a firm, grapefruit-sized mass in the left upper quadrant. A systolic bruit could be heard over the mass and in the left axilla. An upper gastrointestinal series disclosed anterior displacement of the stomach by a smooth, extrinsic mass. Because of the history of bleeding and the presence of a bruit, his physicians at Wadsworth Veterans Administration Hospital referred him to UCLA for celiac angiography. Roentgenograms, made after the injection of contrast material through a catheter selectively placed into the celiac axis, demonstrated an unusual accumulation of the contrast medium adjacent to the distal portion of the splenic artery (Fig. 1*A*). Later roentgenograms in the series showed that there was delayed drainage of contrast material from this area (Fig. 1*B*). A lateral study showed that there was pronounced anterior displacement of the splenic artery and that the accumulation of contrast medium lay posterior to the artery (Fig. 1*C*).

At surgery, a large, tense left upper quadrant pancreatic pseudocyst was found. Laminated clot and brisk arterial bleeding were encountered on opening the cyst. The bleeding came from the splenic artery which coursed along the wall of the cyst. Nine units of blood were administered at surgery. Splenectomy was performed and the cyst was drained externally.[11]

Case II. C.C., a 30 year old Negro male, was admitted with complaints of nausea, vomiting and abdominal pain. The patient had had many previous admissions for gastrointestinal bleeding and for pancreatitis. A vagotomy and pyloroplasty were done at the time of a previous admission. Physical examination disclosed upper abdominal and peri-umbilical tenderness. There was an ill-defined, pulsatile epigastric mass over which a bruit could be heard.

Because of the clinical suspicion of arterial involvement by a pancreatic pseudocyst, the patient was referred for celiac axis angiography. Selective celiac angiography revealed cephalad displacement of the proximal portion of the splenic artery (Fig. 2*B*). The splenic artery was greatly narrowed and there was a rounded accumulation of contrast material in the area of displacement (Fig. 2*A*). A later roentgenogram in the series showed that there was delayed disappearance of the contrast medium (Fig. 2*C*). Also, there appeared to be collateral blood flow to the spleen, predominantly from the left gastroepiploic artery, apparently because of the pronounced proximal narrowing of the splenic artery. At surgery, a 4×8 cm. mass was found, which was thought to be a pancreatic pseudocyst.[11] Ligation of the splenic artery at its origin and splenectomy were performed. No drainage procedure was attempted. The patient returned to the hospital shortly after discharge with recurrent difficulties, which have continued to the present time.

SUMMARY

Serious gastrointestinal bleeding is common in patients with chronic pancreatitis and pancreatic pseudocysts. In many instances, the bleeding is the result of other conditions in the gastrointestinal tract such as peptic ulcer disease. However, pancreatic pseudocysts may produce serious gastrointestinal hemorrhage by erosion of adjacent blood vessels. Two cases in which such lesions were associated with bruits were studied angiographically. In each of these cases, an erosive change of the splenic artery was demonstrated.

Selective celiac angiography is a safe and simple procedure which may provide the surgeon with valuable information in the management of these difficult cases.

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Vol. 99, No. 3

THE SPONTANEOUS DISAPPEARANCE OF GALL STONES

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THE rare reports of the spontaneous disappearance of calculi from the gallbladder do not attest to the frequency with which this might occur. It has been known since the 17th century that calculi within the collecting system structures of the biliary tract could pass from the gallbladder through the extrahepatic biliary radicles into the intestine in the absence of fistula.[5] In the 18th and 19th centuries, additional reports by other investigators indicated that this could happen painlessly.[10,16,19,24]

REPORT OF CASES

CASE I. P.P. A 26 year old female stated that 2½ years ago, immediately following the birth of her second child, she experienced an acute attack of right upper quadrant pain with nausea and vomiting. A roentgenographic examination performed in the hospital on September 23, 1963 showed a nonfunctioning gallbladder. A repeat study using a double dose of the contrast material on September 24, 1963 revealed a poorly functioning gallbladder with many tiny calculi (Fig. 1*A*). The patient elected to defer surgery and for the past 2 years has been completely asymptomatic. In January, 1966, the patient saw another surgeon for evaluation for possible operation despite the asymptomatic interval. The surgeon recommended repeat gallbladder series and on January 17, 1966 a gallbladder study was performed using 6 gm. of telepaque, which proved to be normal. On January 21, 1966 a repeat examination using a lesser amount of the contrast material was performed. Delayed, decubitus and many erect roentgenograms failed to reveal any evidence of calculus (Fig. 1*B*).

CASE II. S.S. A 36 year old female was admitted to a local hospital with a history that for 3 months she had an intolerance to fatty foods with intermittent episodes of pain in the right upper quadrant. A roentgenographic examination of the gallbladder on June 26, 1964 showed the presence of many nonopaque calculi within the gallbladder lumen (Fig. 2*A*). A repeat roentgenographic examination of the gallbladder and intravenous cholangiography performed in preparation for surgery on August 24, 1964 failed to reveal any evidence of residual calculi either within the gallbladder or common bile duct (Fig. 2*B*).

The patient's past history was noncontributory. She had had 2 previous pregnancies, the most recent being 30 months prior to the first gallbladder examination.

DISCUSSION

In our first case, the interval between the demonstration of calculi within the gallbladder in the immediate postpartum period and the discovery of their painless disappearance cholecystographically was 2 years, 4 months. In the second case, the interval between the discovery of the biliary calculi and their disappearance cholecystographically was 8 weeks. Again, this was a painless, asymptomatic interval.

Three ways have been described by which calculi might disappear from the gallbladder spontaneously:

1. The calculi might erode through the gallbladder wall, perforate into the gastrointestinal tract and produce an intestinal biliary fistula, permitting calculi to pass into the intestinal tract. The clinical and roentgenographic findings in this acute intra-abdominal episode are characteristic and have been described in detail.[32,35]

2. A number of authors have suggested that since dietary, chemical, metabolic or hormonal factors, in conjunction with or without stasis or infection, are related to the formation of gallbladder calculi, it is probable that the reduction of these lithogenic agents might cause a reduction in the number of calculi or their total disappearance. The dietary investigative work of

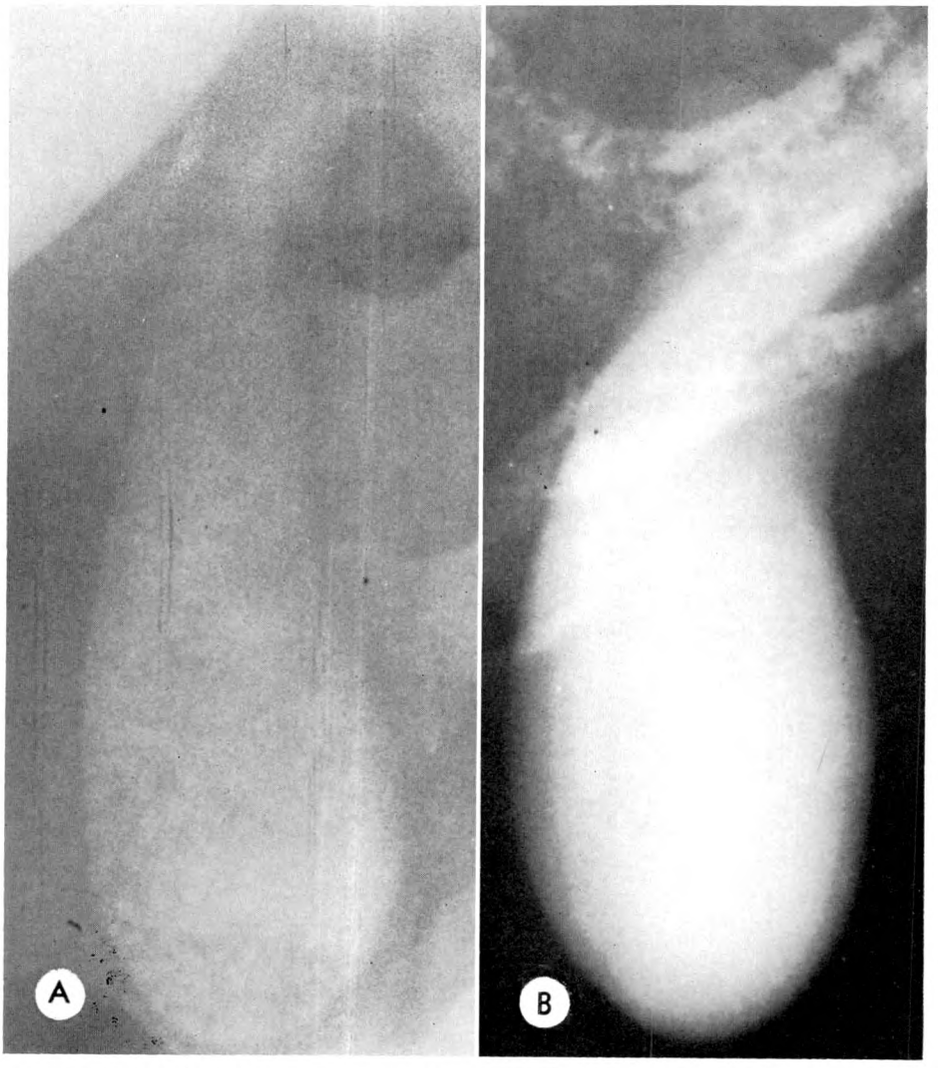


FIG. 1. (*A*) Erect cholecystogram demonstrates numerous small calculi within the fundus of the gallbladder. (*B*) Cholecystogram 2 years 4 months later. No residual calculi.

Christensen and Kristensen[2] provides good experimental evidence of this in hamsters. Other investigators[31] treated 5 patients with bile salts and olive oil and recorded that in 2 cases, the calculi disappeared. Levrat *et al.*[20] noted that the gallbladder calculi in their patient diminished in size and number while being treated with high doses of sodium bicarbonate for peptic ulcer. Linsman and Corday[22] induced hypothyroidism in a patient of theirs with angina pectoris with radioactive iodine and noted that the gall stones, which had been present, disappeared over a period of 4 years. Cole and Harridge,[3] Kommerell and Wolpers,[18] Deuil and Dupuy,[6] Hessen,[12] and Lindrec and Rageot[21] have all noted the possible relationship of the disappearance of calculi in their patients to the bile salt therapy, dietary, cholesterol or metabolic factors. Miller[25] relates the formation of calculi during pregnancy and their disappearance in the postpartum period to the alterations in cholesterol metabolism which are known to occur during pregnancy. It does seem likely that in some cases during preg-

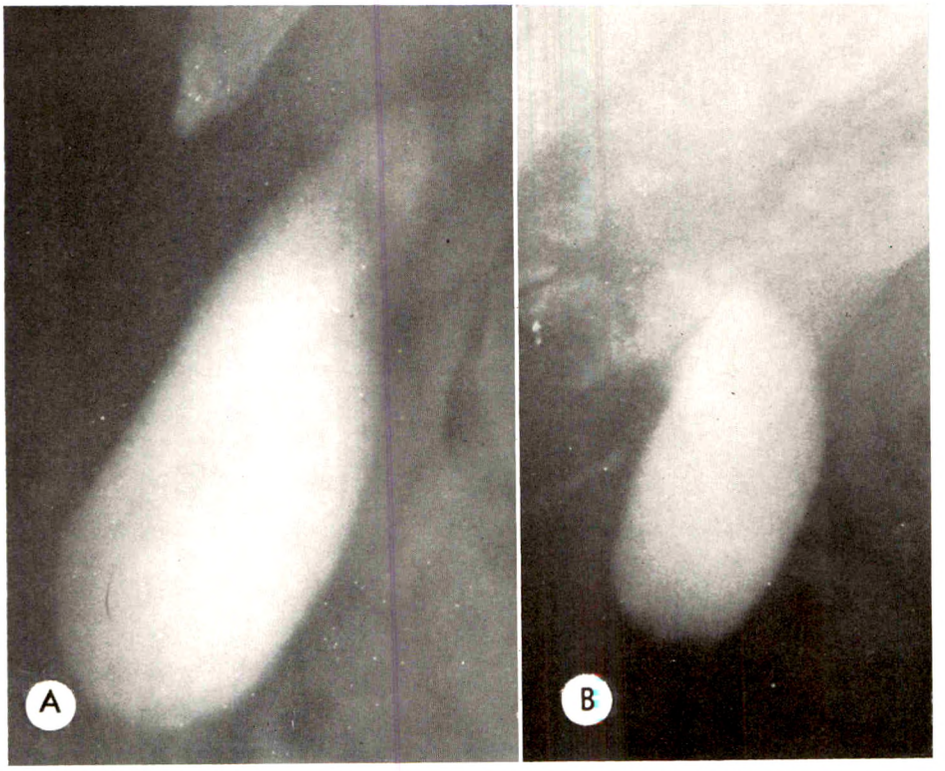


Fig. 2. (*A*) Many nonopaque calculi demonstrated within the gallbladder lumen (*B*) Cholecystogram 8 weeks later. No residual calculi.

nancy the formation of calculi might in part be related to alterations in cholesterol metabolism and stasis. The surgical confirmation of the absence of calculi, however, in as short an interval as 16 days,[7] 8 weeks (our own case), and 10 weeks[28] following cholecystography, would lend more credence to the natural passage of these calculi through the duct system rather than to their chemical or metabolic dissolution.

3. It is the opinion of most investigators that the most likely explanation for the disappearance of calculi from the gallbladder is by means of their passage through the biliary duct system into the proximal small bowel. There have been a number of surgical, clinical and roentgenographic reviews to substantiate this fact. The surgical studies show numerous cases of calculus disease within the cystic and common ducts which have been thought to represent an attempt by the gallbladder to empty these calculi into the intestine.[8,9,23]

The clinical findings of calculi in the feces,[4,13,29] in the vomitus,[13] and in the stomach[30] in the absence of fistula formation have been advanced as further evidence that calculi do pass spontaneously from the gallbladder through the ducts into the gastrointestinal tract. Roentgenographic evidence, supporting this fact, comes from Moreau and Moreau,[26] Schembra,[34] and Richards,[33] who recorded cholecystographically that gallbladder calculi can migrate through the entire duct system from the gallbladder. In Schembra's[34] case, the calculi were seen to pass painlessly during this entire episode.

We believe that in our own cases, the calculi were small enough so that they could have been passed easily through the duct system. We certainly had no clinical or roentgenographic evidence of an internal

biliary fistula, nor was the clinical interval long enough in the second case to suggest the spontaneous dissolution of these calculi.

SUMMARY

The rarity of the reports of the spontaneous disappearance of calculi from the gallbladder is considered. It is suggested once again that gallbladder calculi can and do pass painlessly through the biliary duct system.

The spontaneous disappearance of calculi in the post pregnancy state is again noted. It is recommended that if a significant painless interval elapses between the demonstration of calculi and surgery, particularly if the calculi are small, repeat cholecystography be performed prior to surgery.

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VANISHING PANCREATIC CALCIFICATIONS*

A CASE REPORT

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PANCREATIC calcifications are virtually pathognomonic of chronic pancreatitis. Tucker and Moore[6] have reported the only recorded instance of disappearance of such calcifications. In their patient this was associated with the development of a pancreatic carcinoma. They suggested that such a roentgenographic observation might lead to an earlier diagnosis of carcinoma. A second case of vanishing pancreatic calcifications is herein recorded, but our patient, with chronic pancreatitis, did not concomitantly develop a carcinoma, but rather had a prolonged remission over a period of years prior to her demise.

REPORT OF A CASE

L. T., a 66 year old, Negro female, was admitted to the Edward J. Meyer Memorial Hospital on July 9, 1965 for the sixteenth time. She had a very long and involved medical history. In April, 1955, the patient was seen at another hospital for abdominal pain and gastrointestinal bleeding. She had been a heavy drinker since 1943. Esophageal varices were suspected. Esophagoscopy was negative. Exploratory laparotomy on that admission revealed the presence of an hemangioma of the jejunum which was resected. Abdominal roentgenograms taken during a hospitalization in 1957 demonstrated the presence of pancreatic calcifications. At that time, a sphincterotomy was performed because of persistent pain secondary to pancreatitis. The ingestion of alcohol allegedly ceased that year.

Her first admission to the Edward J. Meyer Memorial Hospital was on March 24, 1958 for gastrointestinal bleeding. Roentgenograms of her abdomen again showed the calcifications in the pancreas (Fig. 1). A gallbladder series revealed a normally functioning gallbladder without calculi.

On January 15, 1960, the patient was admitted for gastrointestinal bleeding. Upper gastrointestinal series demonstrated the presence of a duodenal ulcer; a subtotal gastric resection was carried out. On this admission, she was also started on tolbutamide to correct her newly discovered diabetes. Liver function tests were normal, but the amylase was elevated. She had numerous subsequent admissions for epigastric pain, diarrhea and weakness. In January, 1961, the number of calcifications in the pancreas had diminished (Fig. 2). Ultimately, a scout roentgenogram taken in 1964 (Fig. 3) showed virtually no calcifications. The patient's serum amylase values were elevated on almost all admissions until 1963. From that date forward, the values remained low or normal.

Further medical history showed that sickle cell disease (30 per cent S hemoglobin) was diagnosed in 1960. In 1964, the patient was treated for carcinoma *in situ* of the cervix; total hysterectomy was performed. In that same year, a sigmoid colotomy and polypectomy were performed for a benign adenomatous polyp.

The patient's final admission was July 9, 1965 when she was admitted with weakness, anorexia, and weight loss of 40 pounds. Carcinomatosis was considered. Postmortem examination on August 2, 1965 revealed no malignancy anywhere in the body. The patient did have bilateral bronchopneumonia, nephro-arteriosclerosis and, importantly, a small fibrotic pancreas which histologically showed chronic pancreatitis. A few microscopic calcifications were noted in the parenchyma of the tail. Wirsung's duct was dilated and did not contain any calculi.

DISCUSSION

Chronic pancreatitis is usually divided into two large groups:[1] (1) that associated with biliary tract disease, especially calculi; and (2) that associated with alcoholism, and most usually without demonstrable biliary tract disease. Chronic pancreatitis[5] has also been described as occurring in

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association with certain metabolic diseases including parathyroid adenoma, familial hyperlipemia, hyperlipemia complicating diabetes mellitus, malnutrition and protein deficiency states (usually seen outside of the United States). In certain instances, a familial incidence has been recorded.

Calcification is almost never seen in pancreatitis associated with biliary tract disease, but rather in the so-called "drunkard's pancreatitis." The pancreatic calcifications may occur in the white areas of fat necrosis throughout the parenchyma and the neighboring structures, but more often they are calculi within the ductal system. Usually, at autopsy, myriads of calculi of various sizes are present in the ducts.[1]

The pathogenesis of "drunkard's pancreatitis" has been attributed to the stimulation of secretion of gastric hydrochloric acid which occurs when ethanol is ingested.[1] The hydrochloric acid, in turn, vigorously stimulates pancreatic secretion. Obstruction of the ducts, which may be due to spasm of the sphincter of Oddi, may lead to dilatation and even rupture of ducts or acini. This mechanism will produce stasis and inspissation of the pancreatic secretions, which in turn will often calcify. Usually, these calculi remain in the ductal system of the pancreas and are not passed. Interestingly, Doubilet and Mulholland,[3] in a large series of patients subjected to sphincterotomy, make no mention of any significant postoperative reduction in the calcifications or calculi within the pancreas.

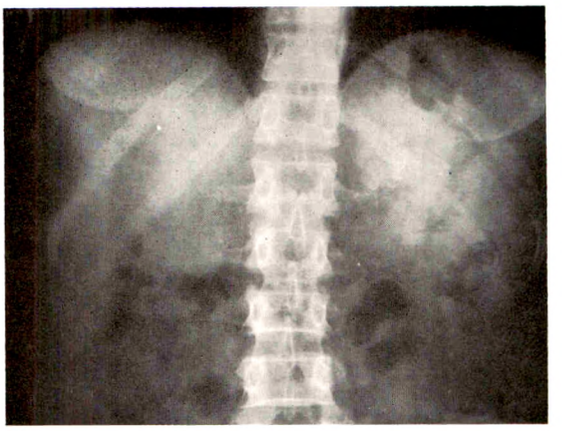


Fig. 2. Scout roentgenogram taken in January, 1961 shows marked reduction in number of pancreatic calcifications.

In the past, the general impression was that calcification indicated a benign lesion and that there was no relationship between pancreatic inflammation and pancreatic carcinoma. However, several authors have suggested that such calcifications are, in fact, a predisposing factor to malignancy. In reviewing 417 patients with carcinoma of the pancreas and 70 patients with chronic pancreatitis, Netto *et al.*[4] found that 6 per cent of patients having carcinoma of the pancreas had had chronic pancreatitis. They also demonstrated that

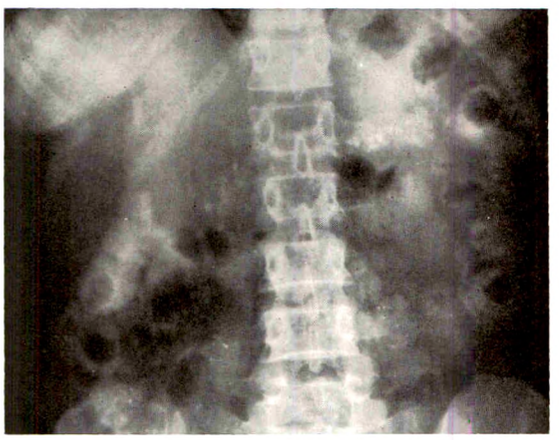


Fig. 1. Roentgenogram of abdomen in March, 1958 shows typical pancreatic calcifications. The gallbladder is visualized at this time.

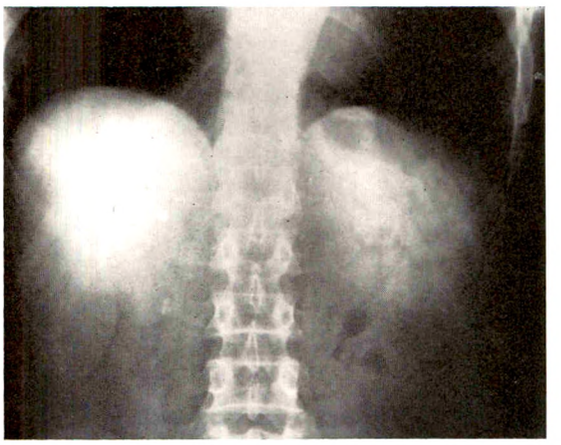


Fig. 3. Scout roentgenogram of September, 1964 shows virtually no residual calcifications.

the incidence of pancreatic cancer in patients with pancreatic calcifications was 25 per cent. This certainly suggests a causal or precursory relationship between the two. Tucker and Moore[6] suggest that the disappearance of these calcifications in such a patient may indicate the development of pancreatic carcinoma. In our case, the patient allegedly ceased the ingestion of alcohol in 1957 which may have contributed to the gradual subsidence of the active pancreatitis and to the passage of the calculi. Only a dilated duct as described in this case would facilitate the passage of intraductal calculi.

Doubilet and Mulholland[3] have shown on the basis of 600 cases, the extraordinary ability of the pancreas to regenerate. They have shown that histologic and functional regeneration will occur in 2 to 4 years, but that the islet cells will not regenerate. In our particular patient, over the last 2 years of her life, a normal serum amylase was maintained but her diabetes remained stationary.

Several authors[2] have recorded surgical removal of the calculi from the ductal system as happened spontaneously in our patient. Link, in 1911, operated upon a patient with chronic pancreatitis and exteriorized the tail of the pancreas to allow external fistula formation. His patient survived 40 years and was well except when the fistula became plugged, this event precipitating another episode of pancreatitis. Other surgeons have split the pancreatic duct in its long axis and removed the intraductal calculi. The tail of the filleted gland has then been anastomosed to a defunctionalized segment of jejunum. In our patient, perhaps aided by the sphincterotomy done years earlier and the cessation of alcoholic ingestion, the dilated ductal system slowly emptied and thus the calcifications vanished.

SUMMARY

A second case of vanishing pancreatic calcifications is reported. Such calcifications, as identified on scout roentgenograms of the abdomen, are virtually pathognomonic of "drunkard's pancreatitis." Reportedly, 25 per cent of patients with pancreatic calcification develop carcinoma. The only previous case of vanishing calcifications was associated with the development of pancreatic carcinoma. The present case represents a contrary experience and was associated only with chronic pancreatitis. The disappearance commenced 4 years after sphincterotomy and the cessation of ingestion of alcohol and was the apparent consequence of the passage of multiple intraductal calculi through the dilated ductal system.

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RENEWED INTEREST IN GASES FOR CONTRAST ROENTGENOGRAPHY

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THE use of gases for contrast roentgenography of organs in body cavities and soft tissue spaces has undergone varying degrees of popularity for a considerable period of time. Stewart and Stein first advocated diagnostic pneumoperitoneum in this country in 1919. Alvarez introduced the use of carbon dioxide in this examination in 1921.[5] In 1921, Carelli injected carbon dioxide intraperitoneally for the demonstration of ecchinococcus cysts and into the perirenal space for visualization of kidneys and adrenal glands.[11] Subsequently, the use of air and oxygen as contrast media in diagnostic radiology enjoyed some popularity until reports of fatalities resulting from their usage curtailed enthusiasm. In a nationwide survey of over 11,000 retroperitoneal pneumographies using air and oxygen, 122 cases of severe gas embolism were reported. Fifty-eight of these cases of gas embolism resulted in death.[4] The use of air and oxygen as contrast media has been discredited in favor of more soluble gases such as nitrous oxide and carbon dioxide.

Recently, we have resumed interest in the use of gas as a contrast medium for the (A) intravascular, (B) intrapleural, and (C) intraperitoneal cavities as well as the (D) retroperitoneal space. The simplicity of the methods of examination has enabled us to employ it as a common adjunct to other conventional roentgenographic procedures. In this report, we will review our present techniques in performing gas contrast roentgenography, demonstrate the application of these methods in various clinical problems, and review experimental data regarding the relative safety of gases.

APPRAISAL OF THE RELATIVE SAFETY OF GASES

CONSIDERATION OF GAS INJECTION INTO SYSTEMIC VEINS

McLelland *et al.*[7] refer to retroperitoneal pneumography using carbon dioxide as a technique that is absolutely safe. Several authors have commented on the safety of carbon dioxide and nitrous oxide because the absorption coefficient of these gases in serum is 20 times greater than that of air or oxygen.[9,12] The relative diffusibility of gases, as stated by Teschendorf,[15] is as follows: "Gas diffusion through a liquid layer is proportional to the absorption coefficient divided by the square root of the density of the gas." At 40° C. the diffusion

TABLE I

DIFFUSION CHARACTERISTICS OF GASES*

Gas	Absorption Coefficient α at 40°C.	Density (d) of Gas at 40°C.	$\frac{\alpha\ 40°C.}{\sqrt{d}\ 40°C.}$	Observed Absorption Time of 100 cc. in Abdomen of Rabbit (hr.)	Observed Absorption Time of 600 cc. in Pleural Cavity of Dog (hr.)
O_2	.02306	1.1055	.02195	20–24	10–12
N_2O	.54435	1.52065	.4414	1–1½	½–1
CO_2	.530	1.520	.4293	¾–1½	Immediate

* From Teschendorf (*Acta radiol.* 1951, *36*, 298).

values for oxygen, nitrous oxide, and carbon dioxide are .02195, .4414, and .4293 respectively (Table 1). The greater solubility of carbon dioxide and nitrous oxide enables these gases to rapidly disappear from a gaseous form in blood vessels. In addition, carbon dioxide combines with alkaline blood buffers, facilitating its disappearance from gaseous form. Air and oxygen, on the other hand, remain as stable bubbles within blood vessels or cardiac chambers.[8] Relatively large amounts of gas, remaining as emboli in the right ventricle, pulmonary artery, and peripheral pulmonary arteries, may blockade blood flow and lead to death. The lethal effects of venous air embolism in dogs was considerably reduced by placing the animals in a left lateral decubitus position. In this position, gas emboli rise away from the outflow tract of the right atrium and right ventricle, allowing a continuity of blood flow from the venae cavae to the pulmonary circulation.[13]

Effects of Gas Injection into Pulmonary Veins

While relatively large volumes of gas injected into the systemic venous system lead to fatal emboli, small quantities of gas-forming emboli in the systemic arterial system may result in death from blockade of coronary or cerebral vessels.[13] The relative safety of carbon dioxide in the systemic circulation of experimental dogs was demonstrated by Moore and Braselton,[8] who injected gas into the pulmonary veins of experimental animals. When air was injected into the pulmonary veins, the resultant gas emboli invariably produced coronary death. Following the injection of carbon dioxide, the bubbles of gas were observed to course into the systemic circulation and enter the coronary arteries, but disappeared into solution before emboli could persist. In a 6 cc. per kg. dosage range, carbon dioxide was well tolerated. One experimental animal was killed by this injection technique with carbon dioxide when the dose was tripled.[8]

Effect of Volumes and Injection Rates on Systemic Vein Injection of Gases

The safety of usage of carbon dioxide in the right side of the heart was demonstrated by injection of carbon dioxide into the systemic veins of dogs in dosages of 7.5 cc. per kg. without producing significant adverse effects.[9] Harvard and co-workers[3] lent credence to the safety of carbon dioxide by reporting the injection into the systemic vein of a dog of 10 liters of carbon dioxide at a rate of 100 cc. per minute without producing demonstrable adverse effect. Tolerance to the intravenous injection of carbon dioxide in other dogs was diminished as the rate of injection was increased. Fatalities in dogs were produced by Harvard *et al.*[3] at an injection rate of 300 cc. per minute.

Safety of Gases Injected Retroperitoneally

In a survey of deaths following retroperitoneal pneumography, Ransom and co-workers[11] report the death of a patient following presacral injection of a total of 1,000 cc. of air. In a review of several other deaths, autopsy findings revealed a disrupted vein at a distance from the needle tip or puncture site used for air injection. Apparently, the introduction of air into the retroperitoneal space expanded the space with sufficient rapidity to disrupt a vein and sustained sufficient pressure in proximity to the vein for the entrance of a fatal bolus of gas.[11] Of considerable interest in this regard is the result of injection of massive volumes of carbon dioxide into the retroperitoneal space of dogs. Ten to 20 liters of carbon dioxide were injected at a rate of approximately 200 cc. per minute without producing a lethal effect. Harvard and co-workers[3] autopsied 1 animal which was subjected to these massive volumes of retroperitoneal carbon dioxide and failed to find evidence of carbon dioxide in the form of gas bubbles in the intravascular spaces.

The following conclusions can be drawn from these experimental data: (1) Nitrous oxide and carbon dioxide, having greater solubility properties than air or oxygen, are

Table II

LETHAL EFFECTS OF INTRAVASCULAR GAS INJECTION IN DOGS

No. of Dogs (7–17.1 kg.)	Gas	Position of Dog	Rate of Injection	Lethal Gas Volume	Median Lethal Volume of Gas
10	Room Air	Supine	100–150 cc./min.	5–40 cc./kg.	200 cc.
10	Nitrous Oxide	Supine	100–150 cc./min.	25–160 cc./kg.	800 cc.
10	Carbon Dioxide	Supine	100–150 cc./min.	24–400 cc./kg.	500 cc.
10	Carbon Dioxide	Left Lateral Decubitus	100–150 cc./min.	75–285 cc./kg.	1,300 cc.

much less likely to form fatal gas emboli when introduced into the intravascular spaces. (2) The safety of even the most soluble gases is related to their rates of intravascular introduction. (3) The left lateral decubitus position allows a greater margin of safety because gas emboli carried to the right heart are buoyed away from the outflow tract of the right ventricle and pulmonary artery. (4) The potentiality of gas emboli occurring during the introduction of massive volumes into the retroperitoneal space has been established by autopsy findings.

We undertook to determine the relative safety of clinically used gases introduced into the systemic veins at injection rates identical to those we employed in our diagnostic roentgenologic procedures.

ANIMAL EXPERIMENTS

Three groups of unanesthetized dogs were injected with air, nitrous oxide, and carbon dioxide at an injection rate of 100 to 150 cc. per minute. The saphenous vein was used as the route of injection after the dogs were placed in a supine position. This position was chosen because it afforded the greatest risk of blockading the pulmonary circulation with gas emboli. Room air produced rapid fatalities in the test animals in concentrations from 5.0 to 40 cc. per kg. The smallest volume producing death with air was 35 cc. (injected into a 7 kg. dog) and the fatal volumes of air ranged from 35 to 400 cc. Injection of nitrous oxide intravenously produced death in concentrations from 25 to 160 cc. per kg. The smallest volume of nitrous oxide producing death was 360 cc. (in a 14.6 kg. dog) and the lethal volumes of nitrous oxide ranged from 360 to 2,100 cc. Carbon dioxide produced death in experimental animals in concentrations ranging from 24 to 400 cc. per kg. The smallest volume of carbon dioxide producing death was 200 cc. (injected intravenously in an 8.4 kg. dog). The lethal volumes of intravenous carbon dioxide ranged from 200 to 4,200 cc.

A group of 10 unanesthetized dogs was injected with carbon dioxide intravenously at a rate of 100 to 150 cc. per minute after being placed in a left lateral decubitus position. The saphenous vein was used as the route of injection. Death was produced in the injected dogs with concentrations ranging from 75 to 285 cc. per kg. The smallest volume producing death was 900 cc. of intravenously injected carbon dioxide in a 9.2 kg. dog. The lethal volumes of carbon dioxide in the left lateral decubitus position ranged from 900 to 2,100 cc. (Table II and Fig. 1).

The results of the data related to the intravenous injection of air into dogs are in accord with those of Moore and Braselton[8] who reported lethal effects following intravenous injections ranging from 6.6 to 15.4 cc. per kg. In regard to the intravenous injection of carbon dioxide, our results are in variance with the general impression that this gas is absolutely safe and that

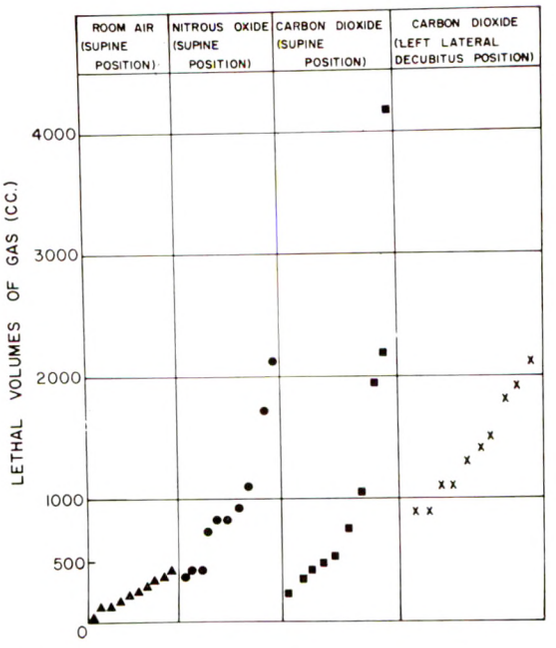


Fig. 1. Lethal intravascular gas volumes in dogs.

astronomical volumes can be injected intravenously at a rate employed clinically without producing adverse effects in experimental animals. The fact that the absorption coefficients of carbon dioxide and nitrous oxide are 20 times those of air and oxygen does not relate directly to the lethal effects caused by intravascular introduction of these gases. In experimental animals, intravenous injection of carbon dioxide and nitrous oxide at a rate of 100 to 150 cc. per minute produced death in concentrations and total volumes only 3 times greater than was produced by air. This margin of safety approximates the criteria applied to the intravascular injection of iodinated contrast media. In employing a method for intrapleural, intraperitoneal, and retroperitoneal examinations, one should concern himself with the avoidance of a direct intravascular injection of gas. It is conceivable that in a confined space, such as the retroperitoneal space, or a body cavity partially obliterated by adhesions, the introduction of gas may result in vessel rupture with subsequent intravascular entrance of gas. With the volumes presently used for these examinations, the margin of safety appears to be a factor of 3, when one relates the weight of experimental dogs to those of human patients. Admittedly, this possibility is remote and no reported fatalities attributable to the use of carbon dioxide or nitrous oxide are found in the literature. It is advisable to employ a technique of injection that allows introduction of gas into a body cavity or retroperitoneal space at a controlled rate. It is essential to use fluoroscopic monitoring during the introduction of the initial volume of gas. When feasible, the initial introduction of gas into a patient in a left lateral decubitus position will add a further margin of safety. The results of our experimental data have not deterred us from continuing and increasing the number of examinations with gas contrast media. The data, however, have served as a guide for care and precautions employed in this method of examination.

A. Intravascular Studies with Carbon Dioxide

The simple method of outlining the right atrial wall has been studied extensively and has been reported by others.[1,9,10,13,16] The rationale for employing this method in detection of pericardial effusion has been substantiated by animal experiments reported by Mellins and co-workers.[6] Opaque pericardial effusions produced in dogs were studied in recumbent, erect, and 4 decubitus positions. Pericardial fluid was demonstrated to collect anteriorly, superiorly, laterally, and to a lesser degree, inferiorly. Almost no pericardial fluid was noted to localize posteriorly. The location of pericardial fluid was not appreciably altered by change in the position of the animal.[6]

Equipment

The following equipment is employed in intravascular carbon dioxide injections:

1. A bottle of 5 per cent dextrose in water connected to intravenous tubing
2. A tank of U.S.P. carbon dioxide con-

nected to a 4 foot length, wide bore, plastic tubing
3. A three-way stopcock
4. A 100 cc. syringe
5. A 6 inch length of wide bore, plastic tubing, to which is wired a male Luer-Lok at one end and a three-way stopcock at the other end. (Connecting tubing attached to a separate three-way stopcock may be used.)
6. An 18 or 20 gauge needle with a 2 cc. syringe (Fig. 2, *A* and *B*).

Following initiation of an intravenous infusion through the short tubing-stopcock arrangement, the carbon dioxide supply is connected by means of a three-way stopcock to the 100 cc. syringe. The syringe system is flushed several times with carbon dioxide and then attached to the intravenous system. One hundred cc. of carbon dioxide is drawn and introduced at a moderate rate of injection.

ROENTGENOGRAPHIC EXAMINATION

Prior to the intravascular injection of carbon dioxide, chest roentgenograms are made in right and left lateral decubitus positions, employing a grid technique. The reason for taking the roentgenogram in the left lateral decubitus position is to verify exposure techniques and positioning. The purpose of the roentgenogram in the right lateral decubitus position is for detection and measurement of the presence of free right pleural fluid. After examination of the preliminary chest roentgenograms, the patient is placed in a left lateral decubitus position prior to the introduction of the intravenous infusion. Following the introduction of 100 cc. of carbon dioxide, 3 films are exposed, changing cassettes manually as quickly as possible.

RESULTS OF INTRAVASCULAR CARBON DIOXIDE INJECTION FOR PERICARDIAL EFFUSION

We wish to re-emphasize the necessity for obtaining a preliminary right lateral decubitus roentgenogram in order to detect the presence of free right pleural fluid. When the patient is placed in a left lateral

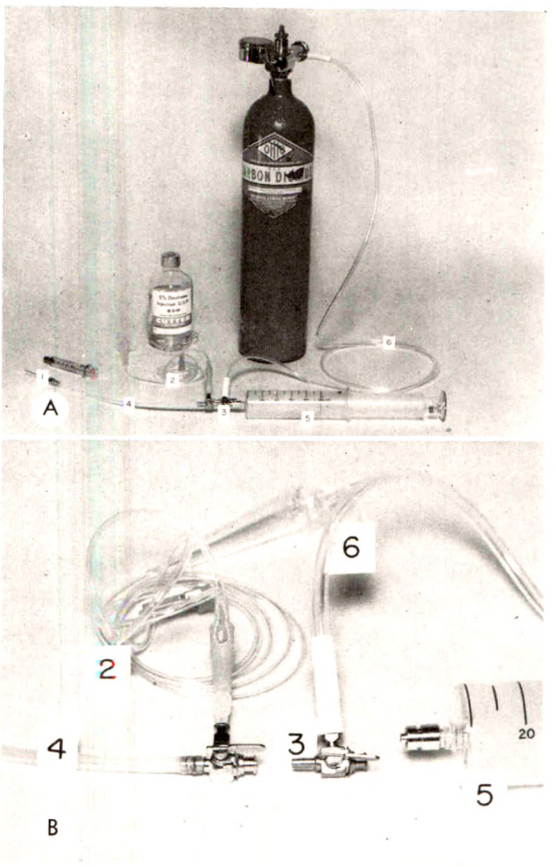


Fig. 2. Equipment employed for intravascular carbon dioxide injections. (*A*) Arrangement of infusion components. (*B*) Detailed description of component connections. (1) Veni puncture needle; (2) intravenous tubing connected to 5% D/W; (3) three-way stopcock; (4) six inch length of plastic tubing with three-way stopcock; (5) 100 cc. syringe; (6) plastic tubing connecting carbon dioxide tank.

decubitus position for the intravascular injection of carbon dioxide and roentgenographic exposure, the forces of gravity and intrapleural pressure may allow free pleural fluid to override the right atrial wall in the form of a mantle, mimicking pericardial fluid. Of course, no difficulty will be encountered in the presence of laterally loculated pleural fluid (as determined by comparison of right and left lateral decubitus roentgenograms) and information may be gained in many instances in which free fluid is present in the right pleural cavity. If a moderate or massive pericardial effu-

sion is demonstrated (right atrial wall measurement over 2 cm. width), the theoretic contribution of the pleural fluid layer to the right atrial wall measurement may be insignificant. On the other hand, demonstration of free fluid in the right pleural cavity does not necessarily interfere with demonstration of a normal right atrial wall thickness. In 1 of our patients, the demonstration of a 12 mm. layer of free pleural fluid did not influence the 5 mm. measurement of the right atrial wall (upper limit of normal for right atrial wall thickness). In another patient, demonstration of a 7 mm. layer of free pleural fluid did not interfere with a 3 mm. measurement of the right atrial wall.

One might expect differences in the right atrial wall measurement related to differences in position of respiratory suspension and differences in cardiac pulsation during roentgenographic exposure. Actually, with the 3-roentgenogram technique, little or no difference in the right atrial wall measurement occurred in measured thicknesses under 10 mm. In measured thicknesses between 10 and 20 mm., a 5 to 20 per cent variation was encountered. Over 20 mm. thickness, the degree of variation in measurement increased, but had no relevance to the clinical problem. Because of the rarety of indecision in determining the presence or absence of free pericardial fluid, the 3-roentgenogram technique is thought by us to be a satisfactory method of examination. There appears to be little necessity for the routine employment of a rapid film changer. The 3-roentgenogram technique demonstrated important differences in measurement at the most lateral and the most inferior margins of the right atrial wall, enabling differentiation of free pericardial fluid from pericardial thickening. If a right atrial width exceeding 5 mm. is nonuniform, that is, wider at the junction of the right atrium with the inferior vena cava than at the lateral-most portion of the right atrium, free pericardial fluid is present. A uniform increased width of the right atrial wall does not permit differentiation between pericardial fluid and thickening. However, a width greater than 20 mm. increases the likelihood of free pericardial fluid, regardless of the uniformity of wall thickness.

With the employment of the 3-roentgenogram technique, 30 of the last 35 patients examined by intravascular carbon dioxide demonstrated filling of the hepatic veins with gas. In 2 of the patients in whom hepatic veins were not filled with gas, obstruction by thrombi or tumor was strongly suspected clinically. We believe, therefore, that the incidence of hepatic vein filling with gas is between 85 to 90 per cent of the patients examined. The intravascular injection of carbon dioxide appears to hold promise as a screening or definitive method of examination for hepatic veins. In this regard, the employment of a rapid film changer may enhance the likelihood of demonstration of patent hepatic veins. Failure of visualization of hepatic veins by intravascular injection of carbon dioxide may be considered as presumptive evidence of anatomic alteration of these structures, necessitating selective catheterization and visualization with opaque contrast medium (Fig. 3 and 4).

B. INTRAPLEURAL CARBON DIOXIDE INJECTION

Intrapleural injection of carbon dioxide deserves mention because of its many applications to clinical problems. Carbon dioxide appears to be the most suitable gas because of its rapid absorption from the



FIG. 3. Case 1. Intravascular carbon dioxide injection demonstrating hepatic vein filling with gas.

pleural space, minimizing patient discomfort during the procedure, and its wider margin of safety in case of accidental pulmonary vein injection.[8]

METHOD OF EXAMINATION

The patient is sedated with barbiturates prior to the examination. The tubing-syringe system employed for intravascular carbon dioxide injection is applicable for this procedure, omitting the intravenous infusion component. A $3\frac{1}{2}$ inch, No. 20, disposable needle, having a short bevel, is introduced into the pleural cavity while the patient is requested to suspend voluntary respiration. The carbon dioxide injection system is flushed several times, following which 50 to 100 cc. of gas is introduced into the pleural cavity. The patient is again requested to suspend voluntary respiration during the injection of the initial volume of gas. The position of the needle and the direction of gas diffusion is determined by fluoroscopic observation. With continued fluoroscopic monitoring, 300 to 1,000 cc. of carbon dioxide is introduced into the pleural space. Chest roentgenograms are made in multiple positions. The absorption of gas is so rapid that, in many instances, re-injection is necessary in order to obtain a suitable number of roentgenograms. This method of intrapleural carbon dioxide examination is easily carried out in conjunction with diagnostic or therapeutic thoracentesis. If the thoracentesis is performed on the roentgenographic table, the carbon dioxide injection system can be attached to the thoracentesis needle and gas can be introduced following removal of pleural fluid.

Intrapleural carbon dioxide roentgenography is the most reliable roentgen method of determining the relationship of peripheral pulmonary mass lesions to the parietal pleura. It has shown surprising results in demonstrating otherwise unrecognized small, subpleural metastases. The method also promises to serve as a valuable procedure in the investigation of unexplained pleural effusions. Often, the nature of pleural densities, detected on routine chest roentgenograms, which cannot be altered by attempted thoracentesis, can be studied with carbon dioxide introduced into the pleural cavity (Fig. 5, *A*, *B* and *C*; Fig. 6, *A* and *B*; and 7, *A*, *B* and *C*).

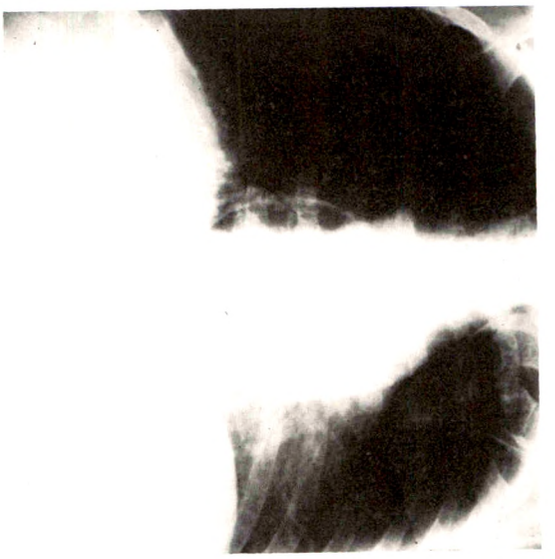


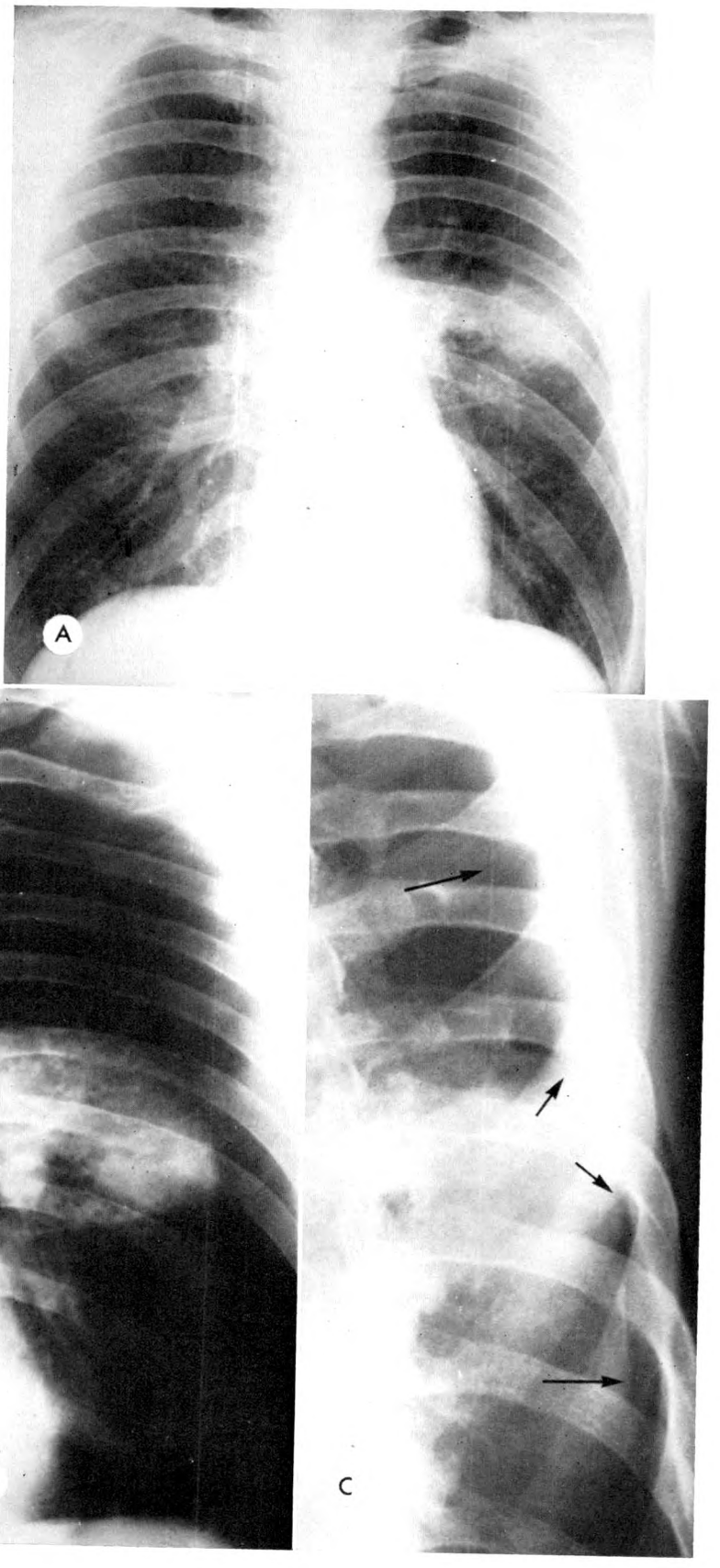
Fig. 4. Case 11. Intravascular carbon dioxide injection in a 42 year old Negro woman whose clinical diagnosis was hepatoma. Note failure of filling of hepatic veins with gas despite adequate volume of carbon dioxide in the right atrium.

C. PNEUMOPERITONEOGRAPHY

Although therapeutic pneumoperitoneum has been widely used in the past, diagnostic pneumoperitoneography has enjoyed sporadic popularity.[5,14] The only contraindication to the usage of diagnostic pneumoperitoneography is in patients with cardiac insufficiency whose cardiac status may be compromised by elevation of the domes of the diaphragm.

METHOD OF EXAMINATION

Premedication with barbiturates and analgesics or narcotics is advised. The abdominal wall is examined for wounds or other signs of potential small bowel adherence to the parietal peritoneum.[14] The urinary bladder should be empty. A $3\frac{1}{2}$ inch, disposable, 18 gauge needle is introduced into the left lower quadrant of the


A
B
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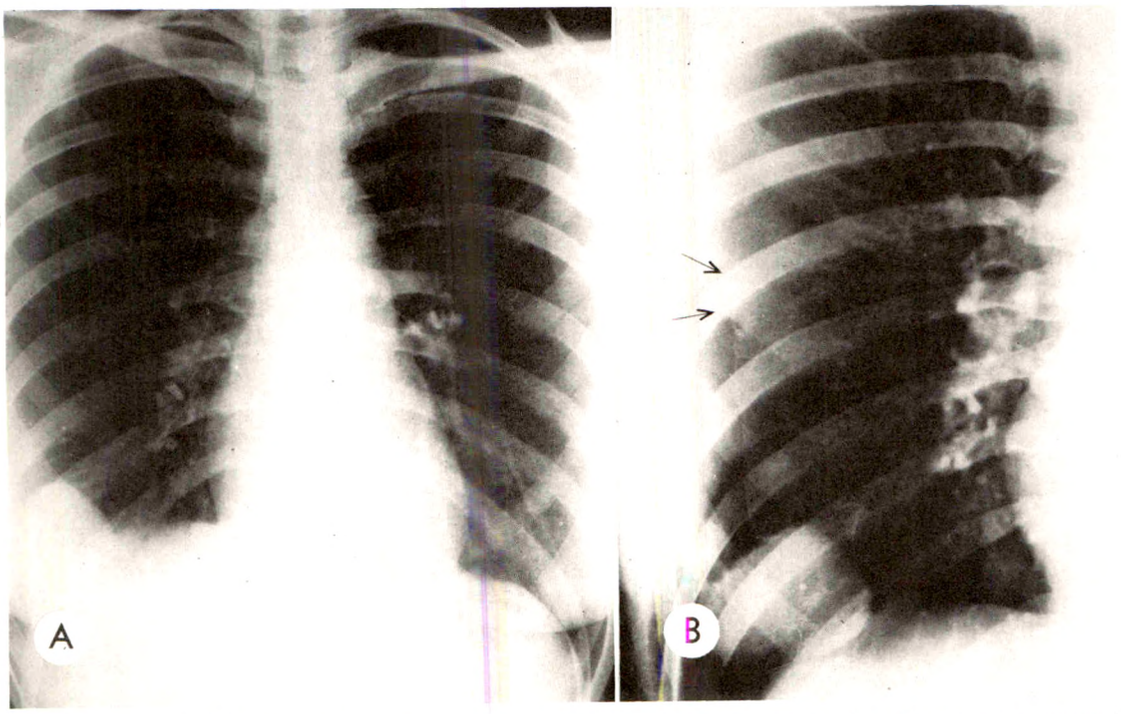


Fig. 6. Case IV. (*A*) Chest roentgenogram of a 24 year old white woman from whose face a malignant melanoma had been resected 1 year ago. The patient complained of right pleuritic chest pain. The presence of a peripheral mass density in the lateral costal margin was equivocal. (*B*) Diagnostic pneumothorax with 300 cc. of carbon dioxide clearly demonstrates the presence of a pleural metastasis laterally (arrows).

abdomen, approximately 2 finger-breadths below and lateral to the umbilicus. The injection system employed is identical to that described for intrapleural carbon dioxide injection. After introduction of the needle into the peritoneal cavity, the carbon dioxide system is flushed and attached to the needle. One hundred cc. of gas is introduced at a moderate rate and the roentgenographic table is tilted so that the patient is in a near vertical position. Care must be taken in supporting the patient as, in many instances, the patient will give the appearance of being hypotensive. This should not cause undue alarm because the reaction is temporary. Seven hundred to one thousand cc. of carbon dioxide is introduced with fluoroscopic monitoring. Roentgenograms are made in multiple positions: prone, supine, cross-table lateral prone and supine, and erect in anteroposterior and oblique positions.

Diagnostic pneumoperitoneography is useful in the study of the size, shape, and position of abdominal viscera. It is also helpful in determining the presence, location, and extent of adhesions. Intraperitoneal masses can be differentiated from

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Fig. 5. Case III. (*A*) Chest roentgenogram of a 35 year old white man admitted because of weight loss and cough. A cavitating mass lesion is demonstrated in the superior segment of the left lower lobe. (*B*) Diagnostic pneumothorax with 400 cc. of carbon dioxide emphasizes the presence of cavitation. (*C*) Left anterior oblique roentgenogram demonstrates extension of the mass to the adjacent pleural surfaces (short arrows). Note the free margin of the remainder of the lung (long arrows).

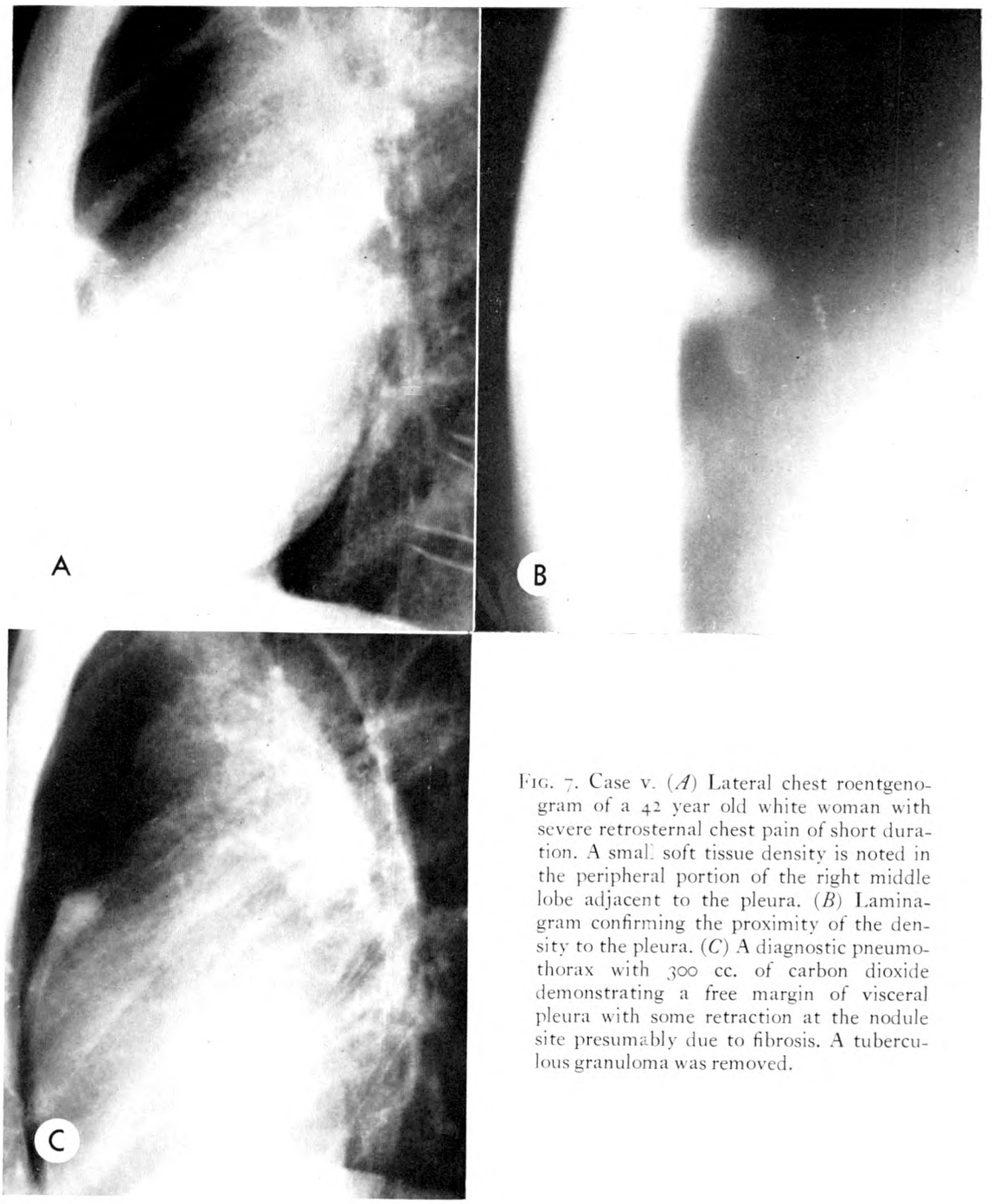


FIG. 7. Case v. (*A*) Lateral chest roentgenogram of a 42 year old white woman with severe retrosternal chest pain of short duration. A small soft tissue density is noted in the peripheral portion of the right middle lobe adjacent to the pleura. (*B*) Laminagram confirming the proximity of the density to the pleura. (*C*) A diagnostic pneumothorax with 300 cc. of carbon dioxide demonstrating a free margin of visceral pleura with some retraction at the nodule site presumably due to fibrosis. A tuberculous granuloma was removed.

retroperitoneal masses, their relationship to other structrues can be determined and their resectability may be ascertained.[5,14] Diagnostic pneumoperitoneography holds promise for the detection and demonstration of subdiaphragmatic collections. The presence or absence of diaphragmatic perforation may be demonstrated (Fig. 8; 9, *A* and *B*; 10, *A* and *B*; and 11, *A* and *B*).

D. RETROPERITONEAL PNEUMOGRAPHY

Anatomic considerations of the retroperitoneal space have been discussed by McLelland and co-workers.[7] Attention has

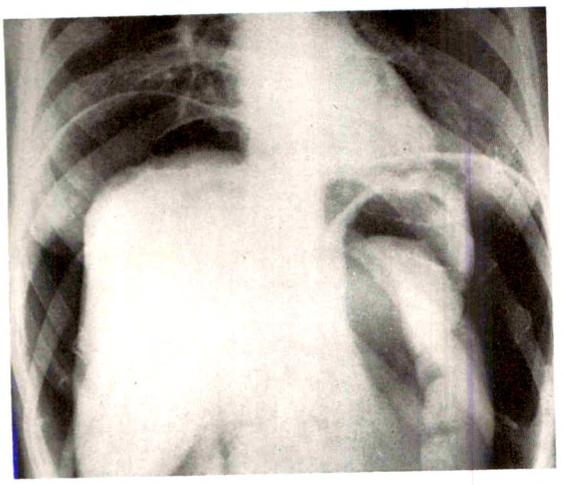


Fig. 8. Case vi. A diagnostic pneumoperitoneum employing carbon dioxide clearly demonstrates the outline of solid and hollow viscera.

been drawn to the possibility of an adrenal gland occupying any position from the upper pole of either kidney to the hilus. The adrenal gland may be loosely related to the kidney and readily separated by gas insufflation or the gland may be intimately attached to the renal outline. Failure of demonstration of an adrenal gland is not necessarily an indication of aplasia.[2]

Method of Examination

Premedication with barbiturates and narcotics is advised. The patient is asked to assume a fetal position on his side with his back to the examiner. If the right side of the retroperitoneal space or if both sides of the retroperitoneal space are of diagnos-

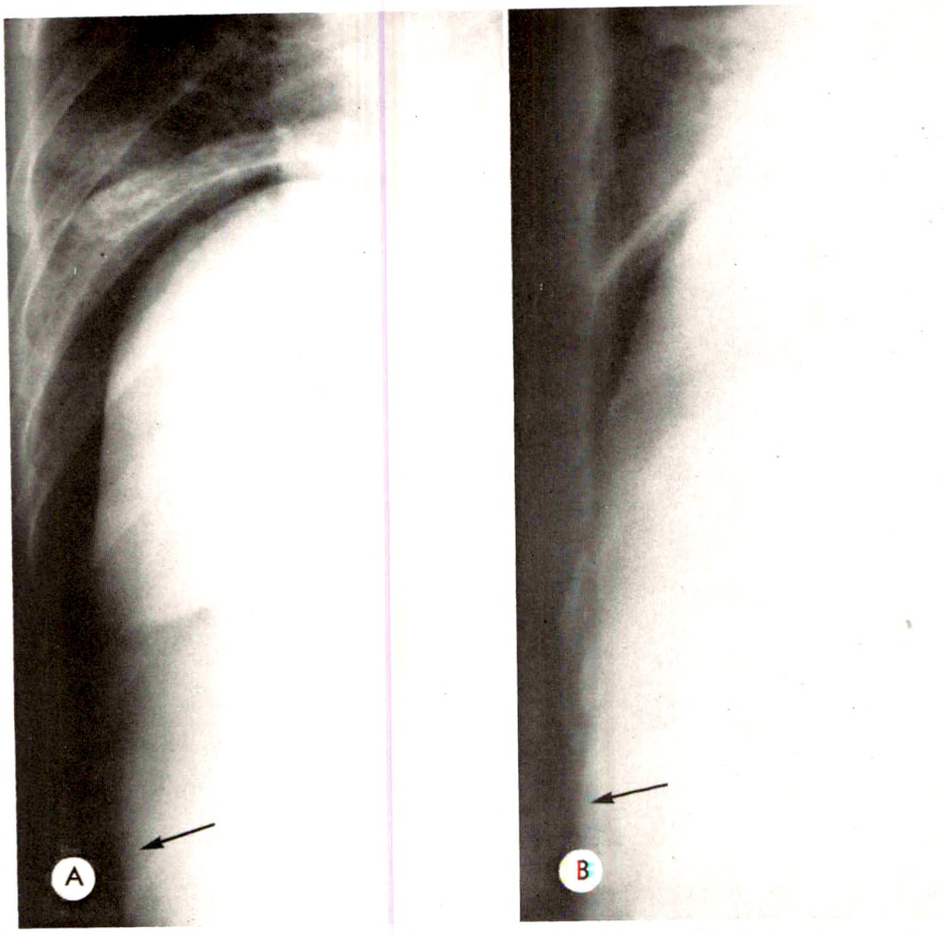


Fig. 9. Case vii. Intraperitoneal carbon dioxide insufflation in a 66 year old white woman with a 6 week history of severe epigastric pain. Clinical evaluation resulted in a tentative diagnosis of hepatoma. (*A*) Roentgenogram in the left anterior oblique projection demonstrates a smooth lateral liver margin (arrow). (*B*) Roentgenogram in the left posterior oblique projection demonstrates tumor nodules forming a portion of liver surface (arrow). A hepatoma was found at laparotomy.

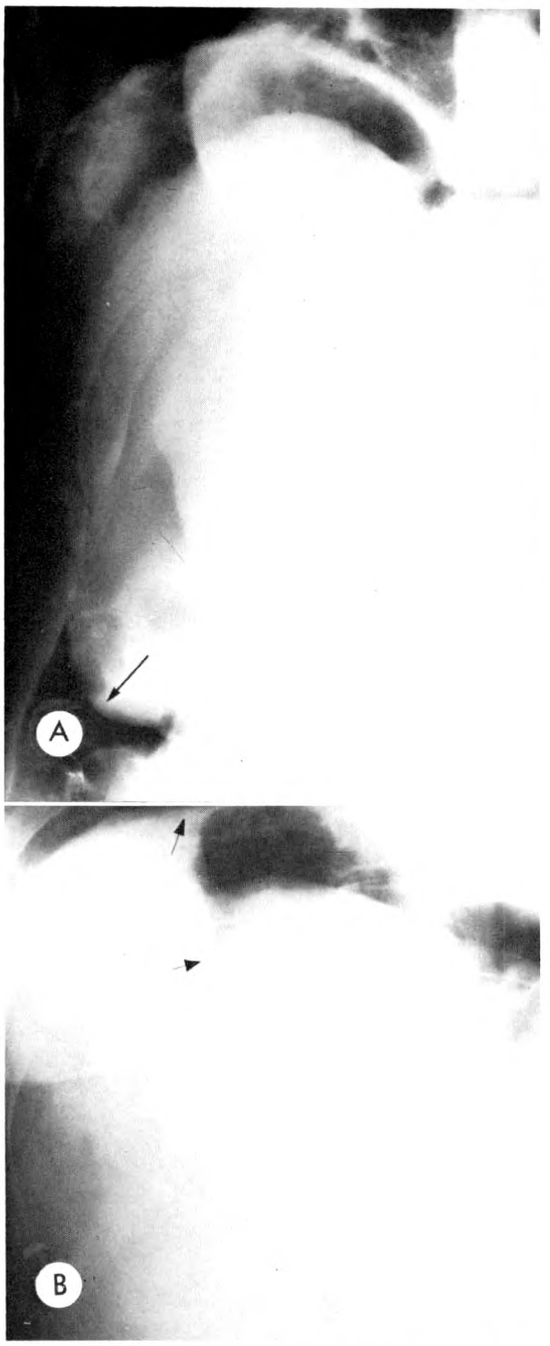


FIG. 10. Case VIII. A 64 year old woman admitted because of recent onset of right pleuritic chest pain. Fourteen months previously, a hysterectomy yielded a low grade leiomyosarcoma. (*A*) Diagnostic pneumoperitoneum with 700 cc. of carbon dioxide. Patient in left anterior oblique position. Demonstration of a mass extending from the caudal portion of the liver (arrow). (*B*) Supine position. Demonstration of a mass extending from the liver to the lateral portion of the right dome of the diaphragm (arrows). At laparotomy, metastatic leiomyosarcoma involving the right lobe of the liver and adjacent portion of diaphragm was found.

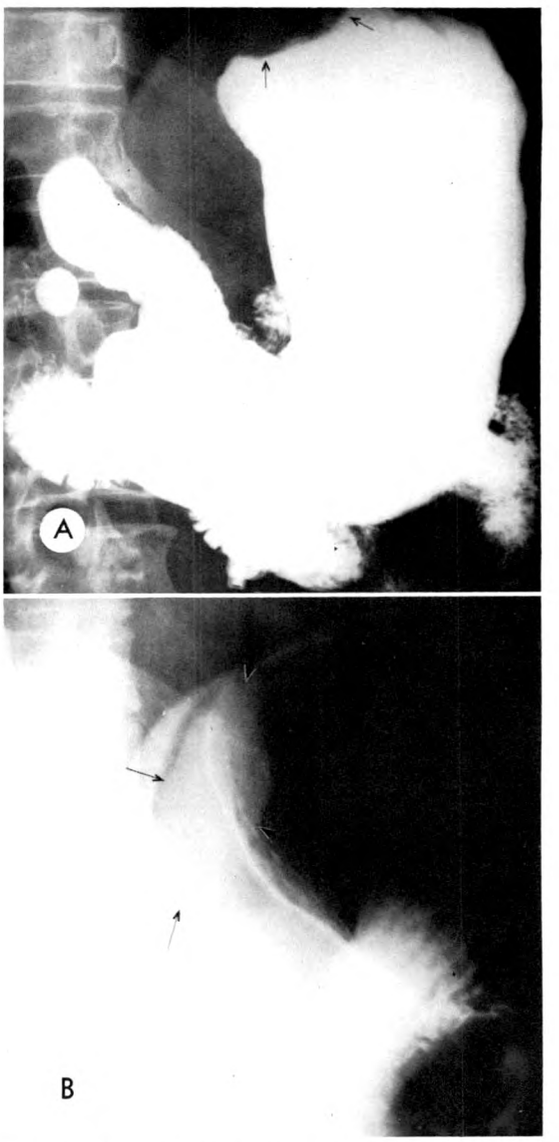
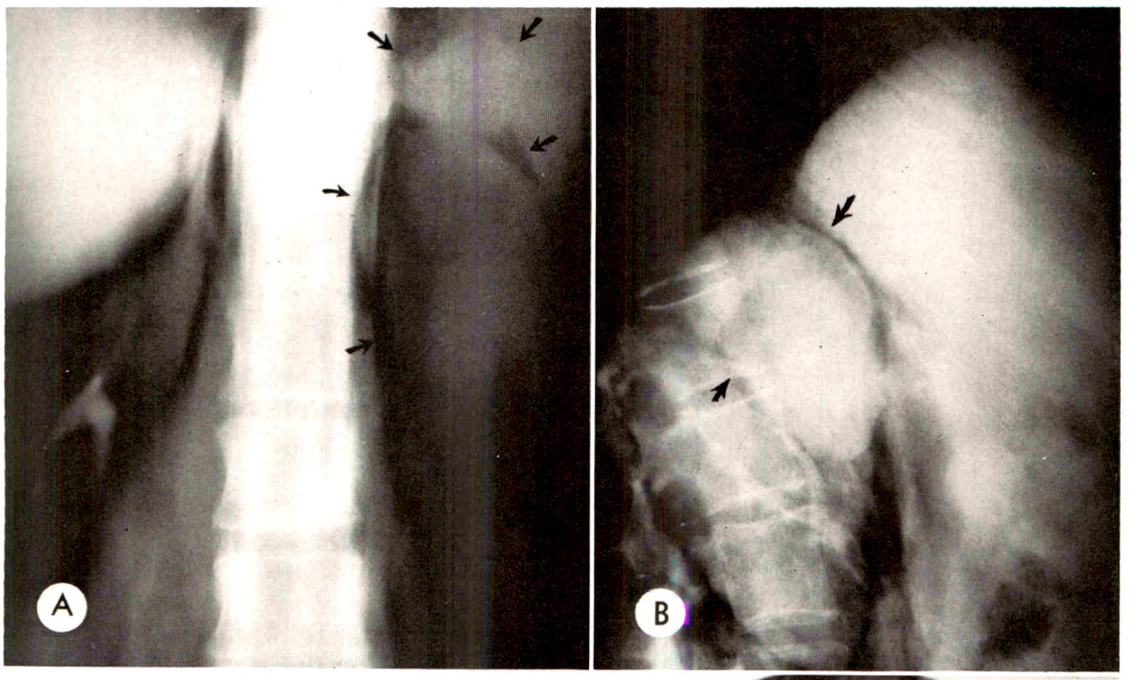


FIG. 11. Case IX. A 59 year old white man with epigastric pain of short duration. (*A*) Prone oblique roentgenogram of stomach filled with barium, demonstrates deformity of the fundus (arrows). (*B*) Diagnostic pneumoperitoneum with 500 cc. of carbon dioxide demonstrates oval shaped soft tissue density which could be separated from the gastric fundus. The mass was believed to represent an accessory spleen (arrows).



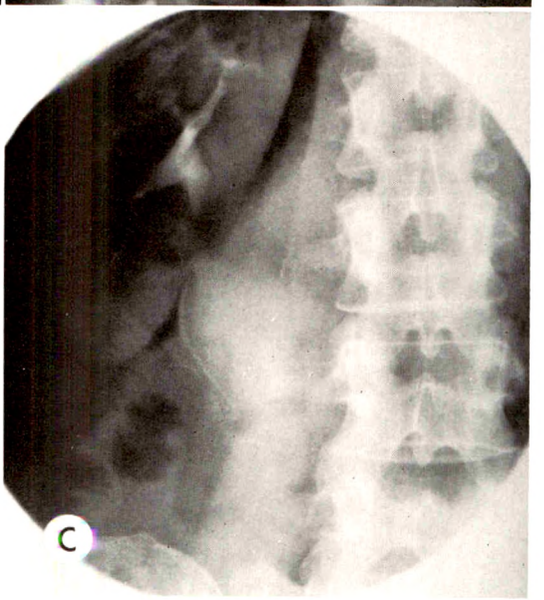


FIG. 12. Case x. A 37 year old white woman was admitted for evaluation of Cushing's syndrome. (*A*) Retroperitoneal pneumogram with 800 cc. of carbon dioxide demonstrates a left suprarenal mass (arrows) and a normal sized right adrenal gland. The psoas margin is clearly defined on the left and obliterated on the right side. (*B*) Lateral roentgenogram demonstrates separation of the left suprarenal mass (arrows) from the kidney. (*C*) Detailed view of the right-sided mass demonstrating its relationship to psoas margin and medial border of right kidney. At exploration, an adrenal cortical adenoma was removed from the left side and a lymphangioma was removed from the right retroperitoneal space.

tic interest, the patient is positioned with the left side dependent. A $3\frac{1}{2}$ inch, disposable, 18 gauge needle is introduced anterior to the tip of the coccyx. The needle is directed posteriorly into the hollow of the sacrum. The needle is introduced for a depth of approximately 2 inches. Introduction of the needle to a greater length occasionally results in injection of gas into the peritoneal cavity. If this occurs, the examination should be deferred until the gas is entirely absorbed. Attempts to localize the needle by introduction of a finger in the rectum are usually not necessary. It is likewise not necessary to direct the needle so that it lies centrally within the presacral space. Satisfactory visualization of structures on either side is independent of the laterality of the needle position.

After flushing the nitrous oxide system

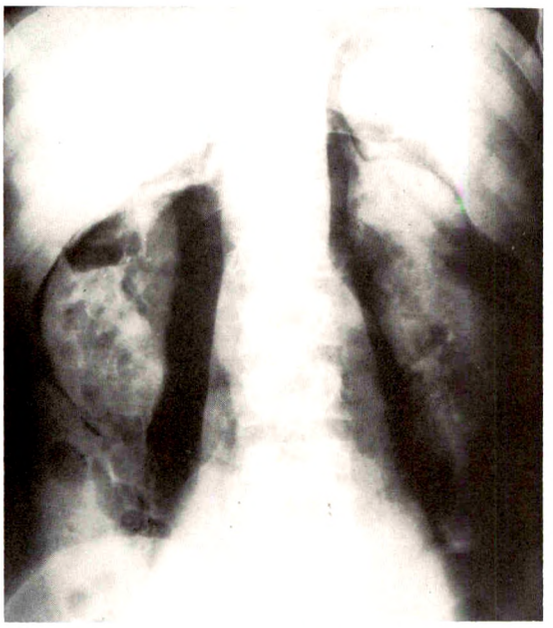


FIG. 13. Case XI. A 14 year old white girl with typical features of Cushing's syndrome for 5 years. Retroperitoneal pneumogram with 700 cc. of carbon dioxide showed a left adrenal mass and a normal sized right adrenal gland. An adrenal cortical adenoma was removed at surgery.

and attachment to the needle, 100 cc. of nitrous oxide is introduced at a moderate injection rate. The patient is turned into a prone oblique position and the roentgenographic table is tilted with fluoroscopic monitoring so that the patient assumes a near vertical position. Satisfactory needle placement is evidenced by the sharply marginated appearance of the psoas muscles and the upper poles of the kidneys. It has been our experience that visualization of retroperitoneal structures is more quickly and easily obtained with the patient in a prone rather than a supine position. Seven hundred to one thousand cc. of nitrous oxide is introduced and roentgenograms are made in multiple positions as the gas shifts easily with change in patient position. The introduction of two needles and replacement by two catheters, one on either side of the midline, as indicated by McLelland and co-workers,[7] is not necessary.

Of 9 patients in whom adrenal cortical tumor was suspected clinically, retroperitoneal pneumography accurately localized and demonstrated the tumor in 6 patients. Two patients in whom no adrenal tumor could be demonstrated, were found to have aldosteronomas, which are invariably too small to demonstrate roentgenographically. Pheochromocytomas were demonstrated without fail. Retroperitoneal pneumography may also be used in the demonstration of renal masses and large lymphogenous masses. Tomography emphasizes the size and position of these masses and may aid in their demonstration (Fig. 12, *A*, *B* and *C*; and 13).

SUMMARY

Four groups of dogs were subjected to intravenous injections of room air, nitrous oxide, and carbon dioxide at injection rates employed clinically in gas contrast roentgenography in order to compare lethal volumes and concentrations. Intravenously injected room air produced death in concentrations similar to those previously reported. Intravenously injected nitrous oxide and carbon dioxide produced death in concentrations and volumes only 3 times greater than air. The volume of carbon dioxide required to produce death was increased 3 times when dogs placed in the left lateral decubitus position were compared with those placed in the supine position. Lethal effects were produced in all dogs injected intravenously with gas at a rate employed in clinical gas roentgenography. Although the absorption coefficients of carbon dioxide and nitrous oxide are 20 times greater than air and oxygen, the safety factor of clinically employed volumes of gas is closer to 3. When introducing relatively large volumes of carbon dioxide and nitrous oxide for intrapleural, intraperitoneal, and retroperitoneal examinations, care should be taken to avoid direct intravascular gas injection, a controlled injection rate should be utilized, fluoroscopic monitoring of the diffusion of the initial volume of gas is advisable, and the left lateral decubitus position should be employed when feasible.

Intravascular injection of 100 cc. of carbon dioxide is a simple and safe method for detecting pericardial effusion. The presence of free right pleural fluid does not necessarily interfere with assessment of right atrial wall thickness. A 3-roentgenogram exposure technique enabled detection of nonuniformity of wall thickness, affording a differentiation between free pericardial fluid and pericardial thickening. The incidence of hepatic vein filling with gas is between 85 to 90 per cent of patients examined and holds promise as a method for roentgen visualization of these structures.

Intrapleural and intraperitoneal carbon dioxide insufflation and nitrous oxide retroperitoneal pneumography are useful and easily performed methods of gas contrast roentgenography.

Gas contrast roentgenography has wide application as an adjunct to conventional roentgenography in solving many clinical problems.

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ECHINOCOCCUS DISEASE*

REPORT OF 112 CASES FROM IRAN AND A REVIEW OF 611 CASES FROM THE UNITED STATES

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ALTHOUGH Echinococcus disease is considered to be a rare entity in the United States, 611 cases have been reported in the literature up to 1965.[1–3,5,7,8,10,11,13,17,18,20–24,27,28,32,34–37,39–42,44,45,49–52,54,56,57,58,60,61] About 50 new cases have been recorded per decade since 1926.[28] The majority of these patients were immigrants, but 45 of the 611 cases may be considered natives of the United States. Native hydatid infections are found more frequently in the state of Mississippi than in other parts of the continental United States;[7,25,26] however, native cases have also been reported from Virginia, Arkansas, Louisiana, Tennessee, Massachusetts and Oregon. Table I shows the epidemiology of this disease as reported from various parts of the world. With an increase in travel to the endemic areas, the possibility of contact with this disease among Americans has increased.[55]

In this paper a review of 112 cases of hydatid cysts which were operated upon at Teheran University Hospitals during the years 1946–1953 is presented. These cases are compared to those reported in the United States from 1822 to 1965.

A comparison of frequency of hydatid cyst in different organs of the body is shown in Table II for both Iran and the United States.

There are two types of Echinococcus disease. The more common form is the unilocular hydatid disease which is caused by the larva of *Echinococcus granulosus*. The rare but much graver form is the alveolar echinococcosis,[29,48,59] which is produced by *Echinococcus multilocularis*. This disease, which acts very similarly to a malignant tumor, is not in the scope of this paper.

Hydatid cysts may be single or multiple and vary very greatly in size. A girl with 13 cysts of the liver was reported by Vergoz and Kourias.[56] Dungal[14] reported a hydatid cyst which was 50 cm. in diameter. The relationship between calcification of the cyst wall and activity of the cyst is the subject of controversy. Some authors[47] believe that calcification does not imply biologic death of the parasite. Others[30] consider it to be indicative of cyst inactivity. In my experience, calcified cysts remained quiescent for many years.

ROENTGEN MANIFESTATIONS OF HYDATID CYST

Although a number of laboratory tests are available for the diagnosis of hydatid

TABLE I

ECHINOCOCCUS DISEASE REPORTED FROM VARIOUS PARTS OF THE WORLD

Country	Author	No. of Cases
U.S.A.	Present report	611
Iran	Present report	112
Argentina	Ferro *et al.*[46]	7,740
Chile	Gajardo-Tobar, Zenteno[48]	147
Uruguay	Ugon[46]	283
England	Wolf[30]	140
Italy	Giromini, Granati[46]	5,048
Austria	Colombani[46]	147
Greece	Geroulanas[46]	4,325
U.S.S.R.	Daniliak[46]	445
Various Countries	Deve[46]	2,727
Australia	Barnett[46]	1,732
New Zealand	Carmalt-Jones[46]	90
Israel	Rakower and Milwidsky[46]	100

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disease,[9,14,33] roentgenologic examination is one of the most helpful diagnostic methods.

HEPATIC CYSTS

The liver is the most common site of involvement (Table II). These cysts are divided into 2 main groups, unruptured and ruptured cysts.

(1) *Unruptured cysts.* Unruptured cysts are also divided into 2 subgroups, depending upon whether or not they are calcified. The roentgen findings in unruptured uncalcified cysts are related to the location of the cyst within the liver. If the cyst is located in the superior portion of the right lobe of the liver, a soft tissue mass, elevating the related portion of the right hemidiaphragm, is seen. The infradiaphragmatic origin of the cyst can be diagnosed by introducing a pneumoperitoneum. At fluoroscopy, large cysts diminish the excursions of the hemidiaphragm. Sometimes discoid atelectasis in the lower lung field is observed. Cysts of the inferior aspect of the liver manifest themselves as soft tissue masses producing extrinsic pressure upon the neighboring organs.

TABLE II

ANATOMIC LOCATIONS OF 112 CASES OF HYDATID CYST COLLECTED BY THE AUTHOR IN TEHERAN, IRAN, AS COMPARED WITH 611 RECORDED CASES IN THE UNITED STATES

Organ Involved	112 Cases in Teheran	596 Cases in U.S.A.*
Liver	54	434
Lung	31	62
Spinal Cord	5	3
Peritoneum	4	52
Body Wall	4	18
Spleen	3	19
Brain	3	7
Bone	2	10
Bladder	2	6
Thyroid Gland	1	0
Kidney	1	25
Breast	1	5
Pleura	1	9
Prostate Gland	0	2
Heart	0	3
Eye	0	1
Ovary	0	1
Uterus	0	1

* In an additional 15 cases the exact location of the cyst is not known. Some of the patients had multiple sites of involvement; therefore, the total number is 658 instead of 596.

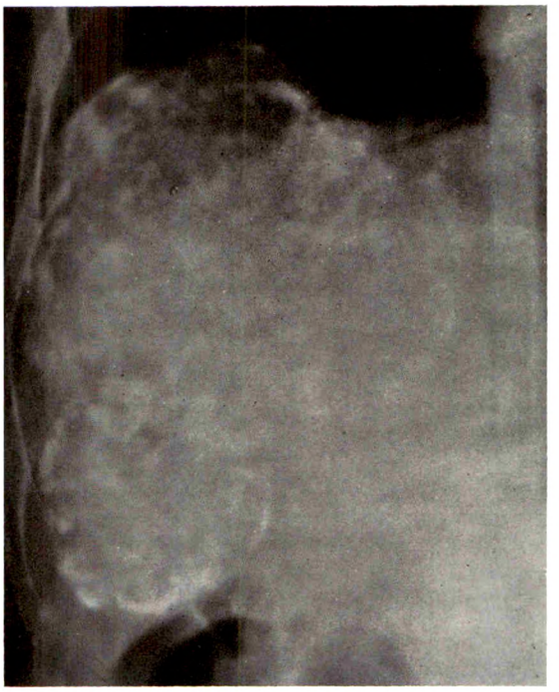


FIG. 1. Calcified hydatid cysts of the liver with a polycyclic appearance related to calcification of the daughter cysts.

Polycyclic calcification due to unruptured calcified cysts is pathognomonic of hydatid liver disease. In these cases, not only the mother cyst is calcified, but most of the daughter cysts as well and have a characteristic appearance (Fig. 1). Lunar calcification is another manifestation of unruptured cysts. Complete egg shell calcification of the cyst wall is also seen (Fig. 2). The differential diagnosis of the calcified hydatid cysts should include other causes of calcification in the right upper quadrant of the abdomen. Among these are calcified gallbladder, gall stones, calcifications within the right kidney, pancreas or adrenal glands, calcified mesenteric lymph nodes and calcification of costal cartilages.

(2) *Ruptured cysts.* Hydatid cysts of the liver may rupture into the pleura, peritoneal cavity or gastrointestinal tract. Rupture into the pleural cavity produces

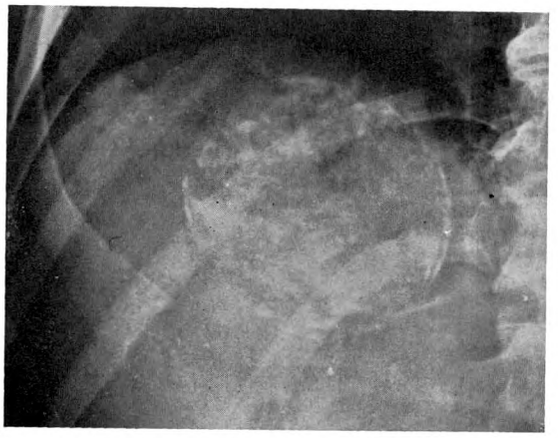


FIG. 2. Egg-shell calcification of a hepatic echinococcus cyst. (Courtesy of Drs. J. Taylor and G. Wohl.)

pleurisy and pneumonitis. Rupture into the peritoneal cavity produces haziness of the abdomen, which is not characteristic of echinococcosis. Rupture into the biliary tract causes nonvisualization of the gallbladder and rupture into the gastrointestinal system produces fistulas. Infection of the cyst is usually secondary to rupture; however, Herbsman *et al.*[21] report a case of a closed liver hydatid cyst infected with Salmonella Saint Paul.

PULMONARY CYSTS

Lung cysts may be central or peripheral, multiple or single (Fig. 3 and 5) and unruptured (Fig. 3 and 5) or ruptured (Fig. 4 and 6).

Roentgen manifestations of echinococcosis of the lung are as follows.

1. Round or ovoid opacities. Pulmonary cysts may be round (Fig. 7) or ovoid (Fig. 5) in appearance. The hydatid cyst may become ovoid on deep inspiration and present a rounded appearance on expiration. This is a useful sign, but it is not characteristic of hydatid cyst alone. It only tells that the pulmonary density is cystic and not solid. Multiple cysts of the lungs (Fig. 3, 4 and 7) are not rare. The differential diagnosis not infrequently lies between hydatid cyst and pulmonary metastasis.

2. The sign of detachment. If the adventitia communicates with the bronchial tree, air will enter between the ectocyst and the adventitia. This will cause a crescentic radiolucent image just above the cyst shadow which has been given different names by various authors.

3. The double arc sign. After the cyst wall is ruptured, air will enter into the cyst and a double arc will be formed, the cyst wall being between the two arcs.

4. The "undulating membrane" or water lily sign. After the cyst wall is detached

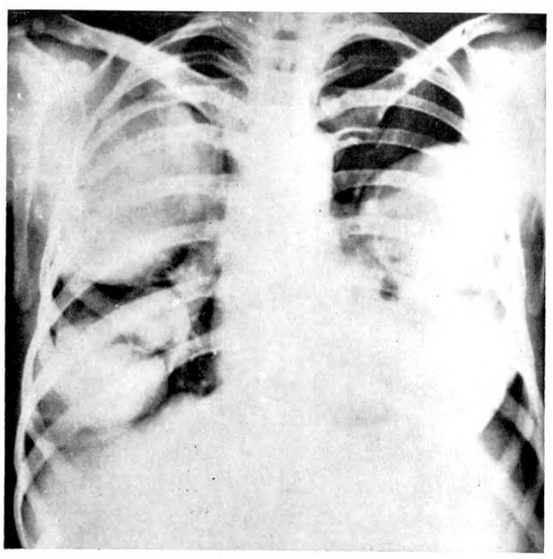


FIG. 3. Multiple pulmonary hydatid cysts.

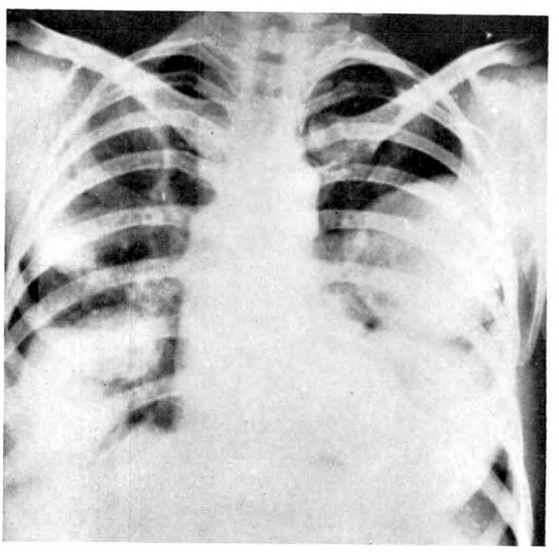


FIG. 4. The same patient as shown in Figure 3 after 2 cysts in the right upper lobe ruptured.

from the adventitia, it covers the remaining fluid within the cyst. At this time, the cyst wall is floating upon the cyst fluid resembling a water lily floating on the water. This is pathognomonic of a ruptured pulmonary hydatid cyst.

5. Abscess formation. After the cyst ruptures it may become infected. An air fluid level will be present within the cyst cavity. The appearance of the cyst is similar to an abscess except for a sharply delineated ring of adventitia covering the cyst cavity.

6. Calcification. Calcification of the lung cyst is unusual. I have not observed a calcified pulmonary cyst; however, this has been reported by Latham.[30]

7. Juxtapleural opacities. Cysts arising from the subpleural portion of the lung may produce hemispherical opacities.

8. Centrally located cysts may be similar to mediastinal tumors. The treatment of pulmonary cysts like that of other organs is surgical removal (Fig. 7 and 8).

PERITONEAL CYSTS

These cysts are usually secondary to cysts of the liver. If the cyst is not calcified, it produces a rounded soft tissue mass. If calcified, it shows either egg-shell (Fig. 9) or polycyclic calcification.

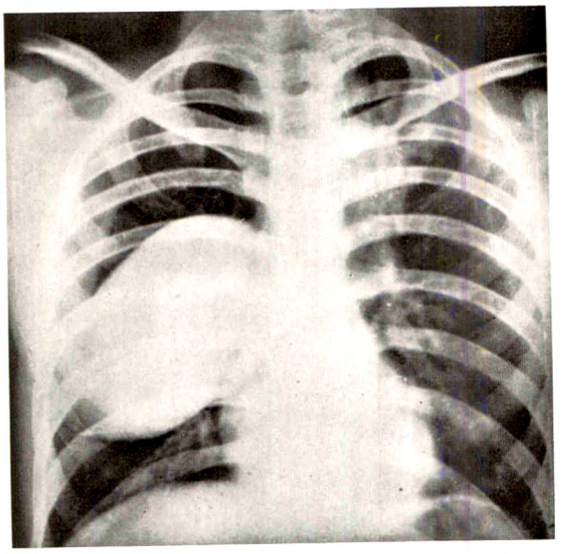


Fig. 5. Ovoid cyst of the right lung before rupture. Changes in the left upper lobe were attributed to a tuberculous process.

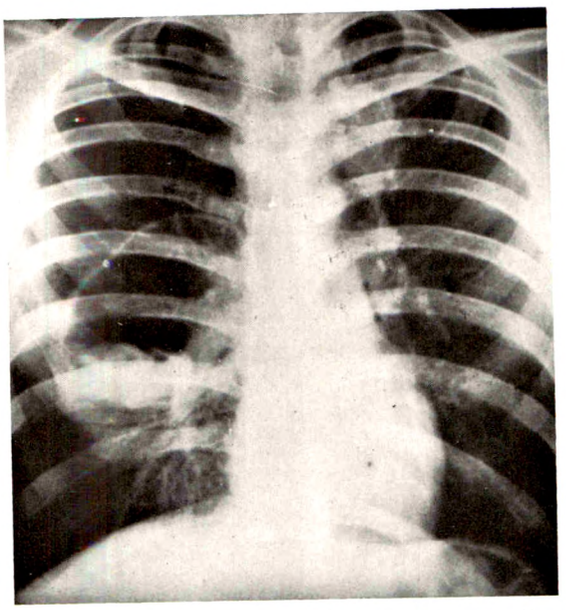


Fig. 6. The same patient as shown in Figure 5 after rupture of the cyst. Note the undulating membrane in the lower portion of the cyst.

RENAL CYSTS

Unruptured and uncalcified cysts on intravenous and retrograde pyelograms present as space occupying lesions. The differential diagnosis includes tumors, solitary cysts, multiple cysts and polycystic disease

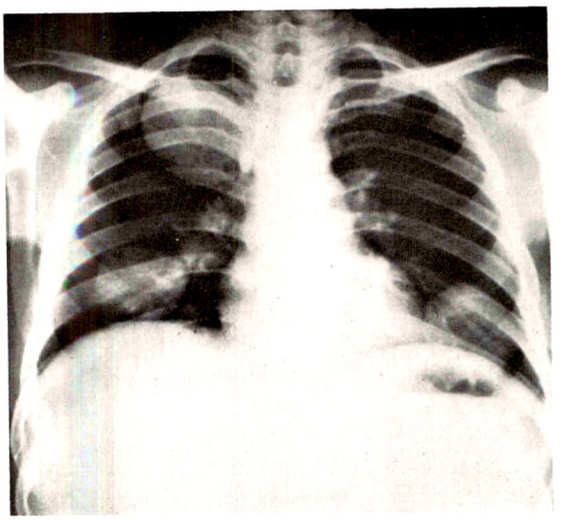


Fig. 7. Multiple pulmonary hydatid cysts before operation.

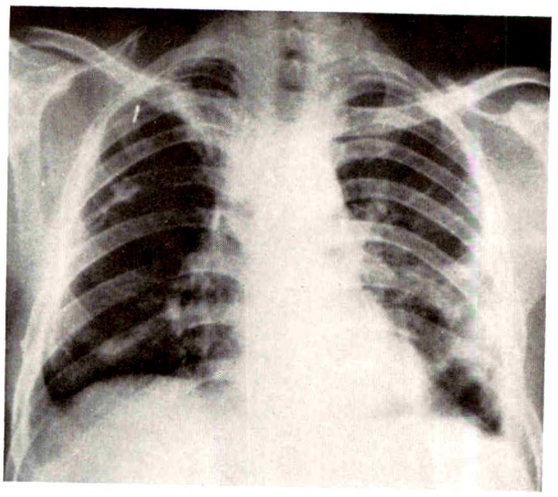


FIG. 8. The same patient as shown in Figure 7 after removal of pulmonary cysts. Changes in the left lower lung field are postsurgical.

of the kidneys. Unruptured and calcified cysts should be differentiated from calcified solitary renal cysts, neoplasm and cavernous renal tuberculosis.

A ruptured cyst presents on intravenous pyelograms as a diverticulum-like structure, connecting with the renal pelvocalyceal system. This has a "wine glass" appearance.[31] Sometimes daughter cysts, in the form of filling defects, may be observed within the opacified cyst. Ruptured cysts may also calcify.

SPLENIC CYSTS

These cysts are either primary or secondary to ruptured liver cysts. If the cyst is not calcified, an enlarged spleen or soft tissue mass attached to the spleen may be found. These cysts produce extrinsic pressure upon the neighboring organs, especially the stomach and the splenic flexure of the colon. If the cyst is calcified (Fig. 9), calcification may be complete, incomplete, or polycyclic. Ruptured cysts of the spleen are similar to those of the liver.

BONE CYSTS

The lesion starts as a small osteolytic process. No periosteal reaction is seen in uncomplicated cysts.[4,31] As the disease progresses, the lesion will take the form of a sharply delineated osteolytic lesion with a soap bubble appearance resembling that of osteoclastoma, aneurysmal bone cyst, and similar lesions. Expansion of the bone may occur at a later stage.[38] The term "ossifluent abscess" is used in the event that the hydatid cyst breaks through the cortex.[31] Pathologic fracture is a common complication.[4] Compression of the spinal cord and complete blockage as demonstrated by myelography[31,47] are common findings with osteohydatidosis of the spine. Secondary infection may further complicate the diagnosis and course of this disease.

CEREBRAL CYSTS

Roentgenograms of the skull may show signs of increased intracranial pressure.[6] Sometimes, curvilinear or amorphous calcification is present. Rarely, an osteolytic lesion of the skull is observed which is often



FIG. 9. Calcified hydatid cysts of the spleen. Note the presence of several small calcified peritoneal cysts.

related to invasion of bone by an adjacent cyst. Multivesicular cysts may have an osseous origin. Air encephalography and cerebral angiography reveal the presence of a space occupying lesion of the brain. Sometimes, during the procedure of ventriculography, air is introduced into the cyst, producing a pneumocystogram (Fig. 10). If the patient is suspected of having a cerebral hydatid cyst, ventriculography must be avoided because of the danger of puncturing the cyst and transplanting the scolices to the other portions of the brain. The Casoni and other laboratory tests are seldom positive because the cyst usually remains intact.

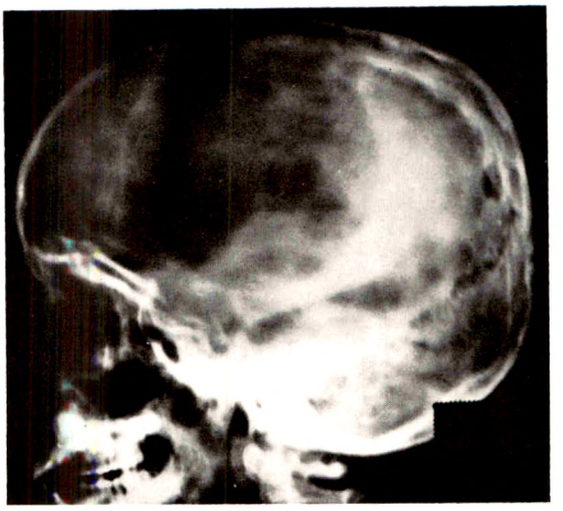


Fig. 10. Incidental pneumocystogram of a cerebral hydatid cyst. (Reproduced with permission from *Journal of Neurosurgery*.)

SPINAL CYSTS

In contrast to the brain, spinal cysts are often extradural and secondary to osteohydatidosis of the spine.[6] The intervertebral disks, capsules and ligaments are resistant to hydatidosis. Extraspinal roentgen findings, such as subpleural cysts and rib erosion, are sometimes present. Myelography may show a partial or complete block to the flow of the contrast medium.

CARDIAC CYSTS

The most common site of involvement is the left ventricle. Gibson[16] found that the left ventricle was involved in 29 out of 48 patients with cardiac cysts. Calcific shadows in the periphery of the heart, in endemic areas, if not due to constrictive pericarditis, should make one suspicious of Echinococcus disease.[9] If the cyst is not calcified, it presents as a rounded soft tissue mass emerging partly from the cardiac silhouette. In this case, the differential diagnosis lies between cardiac aneurysm and hydatid cyst. Angiocardiography may show a rounded filling defect within the contrast column if the cyst is deep enough to bulge into the cardiac chamber.

CYSTS OF OTHER ORGANS

Cysts are seen in almost every other organ of the body. Echinococcus cysts of the head of the pancreas are roentgenologically similar to other cysts.[38] Mediastinal cysts simulate other mediastinal tumors.[43] Cysts of the thyroid,[6] breast,[6] eye,[53] bladder,[6] tongue,[19] and other muscles[6,41] also have been reported.

SUMMARY

One hundred and twelve patients with hydatid cyst who have been operated upon at Teheran University Hospitals, Teheran, Iran, during the years 1946–1953 are reviewed, and compared to 611 cases of hydatid cyst from the United States reported up to 1965.

Roentgen examination is the most helpful diagnostic method for demonstrating Echinococcus cyst.

The liver is the most common site of involvement. Pulmonary cysts are the second in frequency in both series. Hydatid cysts of the liver may produce extrinsic pressure upon the neighboring organs. Localized polycyclic calcification of the liver is characteristic of Echinococcus cyst. Unruptured pulmonary cysts, single or multiple, appear as rounded or ovoid densities. The undulating membrane or water lily sign is pathognomonic of ruptured lung cysts. Pulmonary cysts do not calcify. Hydatid cysts may be found in the peritoneum, kidney, spleen, bone, brain, spine,

heart and almost any other organ in the body. The roentgen manifestations of the cyst in these organs are discussed.

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PERICARDIAL CYSTS AND DIVERTICULA*

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THE classic roentgenographic picture of a pericardial cyst or diverticulum is usually considered to be a round or ovoid shadow or density in the anterior or middle mediastinum adjacent to and blending with the cardiac contour without fluid levels or calcific brim. The mass commonly merges with the cardiac shadow and thus may be unrecognizable in one projection, but in other projections it becomes sharply defined. It is always in contact with the cardiac silhouette.[1–4,7] The differential diagnosis of this roentgenographic picture is extensive,[8] including: lesions of the heart, pericardium and great vessels, mediastinal tumor masses, either congenital or developmental, inflammatory masses, diaphragmatic tumors or eventration, hernias, localized pleural tumors and loculated fluid. Variations of normal such as apical fat pads, rotation of the heart and partial absence of the pericardium can be considered. From a practical point of view a positive diagnosis is often impossible preoperatively; nevertheless, certain roentgenographic findings and special studies may be sufficient to indicate the proper diagnosis.

ETIOLOGY

Authors have traditionally discussed both acquired and congenital etiologies of pericardial cyst and diverticulum. It has been observed by some that localized weakness of the pericardium concomitant with pericardial effusion is the etiologic combination underlying the development of some pericardial diverticula.[5] Others draw a close parallel between pericardial diverticulum and the more common pleuropericardial cyst, which is more generally accepted as congenital in origin. Lomhoff and Stein[5] reported a thin walled pericardial cyst arising from a diverticulum of pericardium which had sealed itself from the pericardial space by obliterative fibrosis at the origin site. Roentgenographically, pericardial cysts and diverticula can appear similar, and etiologically, similarities may exist as well. It would be appropriate, therefore, to discuss both in this paper.

PATHOLOGY

The pericardium is a serous membrane in the form of a closed sac. The connective tissue of its wall is abundantly supplied with elastic fibers lined by an elastic basement membrane supporting a single layer of endothelium. The pericardium consists of two layers: (a) the visceral layer (epicardium) which covers the surface of the heart and the roots of the great vessels (aorta and pulmonary artery) to which it is firmly attached; and (b) the tough parietal pericardium. A small quantity of clear yellow fluid separates the two layers. This outer layer is anchored firmly to the central tendon of the diaphragm and is attached loosely to the sternum anteriorly and to the mediastinal structures posteriorly.

Congenital anomalies of the pericardium are rare. One is a defect or absence of part of the parietal pericardium. A diverticulum of the pericardium may be of congenital origin, but it is probably acquired. It is a pouch-like communication with the pericardial cavity and, in most cases, contains pericardial effusion. If the connecting stalk is wide, the cyst may flatten or become smaller on deep inspiration. This sign, roentgenographically, is often unrecognizable. The wall of the pericardial diverticulum is similar to pericardium except that it lacks the dense bands of collagen fibers, thus resulting in a flexible and flaccid sac. During surgical exposure a tendency of pericardial fluid to flow back

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and forth between the pericardial sac and the diverticulum has been observed. This continual flow may play a role in the enlargement of the diverticulum. The only absolute roentgen sign of a pericardial diverticulum is the disappearance or decrease in size of the cystic mass during an examination when various positions and maneuvers are utilized.

True cysts of the pericardium arise from the parietal portions and have no patent communication with the pericardial sac. They are most common on the right side of the heart shadow or in one of the cardiophrenic angles. On rare occasions, a cyst involving the pericardium may be a true dermoid and contain rudimentary teeth.

The following cases have been selected to illustrate the varying appearance and clinical patterns.

ILLUSTRATIVE CASES

Case 1. This was the second hospitalization of a 31 year old Puerto Rican male who entered with the chief complaint of an asymptomatic mediastinal mass.

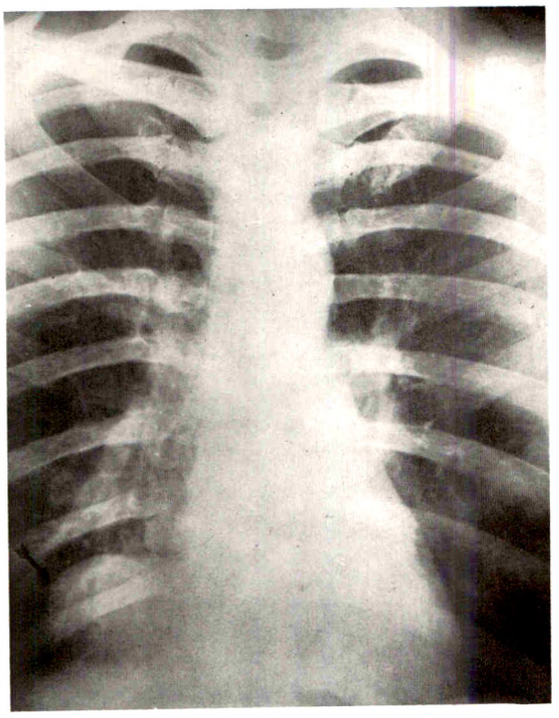


Fig. 1. Case 1. A frontal chest roentgenogram shows a rounded density in the anterior right lower lung field, filling the cardiophrenic angle.

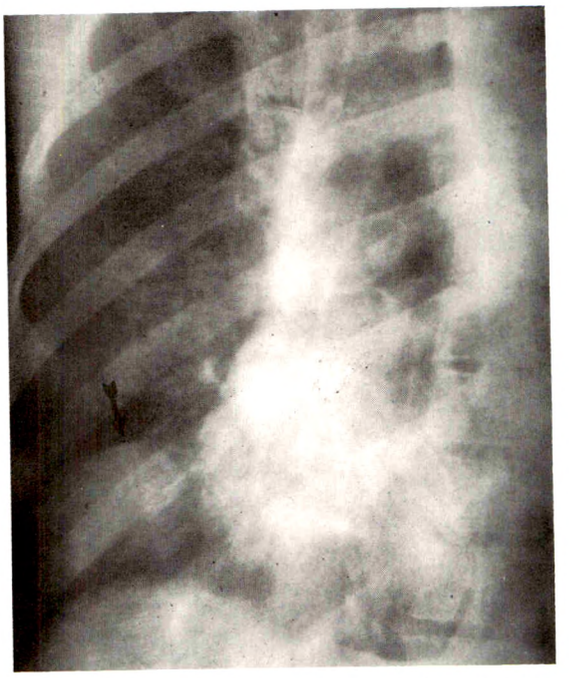


Fig. 2. Case 1. All oblique and lateral views failed to separate the density from the right heart border.

During the patient's previous admission for a right ureteral stone, a routine chest roentgenogram demonstrated a density in the right cardiophrenic angle. It was felt at that time that the diagnosis was most likely a pericardial cyst.

Physical examination was unremarkable.

Chest roentgenogram showed a rounded density in the anterior right lower lung field near the cardiophrenic angle (Fig. 1). Multiple views of the heart showed that the mass was continuous with the pericardium (Fig. 2).

On the third hospital day, the patient underwent a right thoracotomy and a pericardial cyst was noted and excised. The patient made an uneventful recovery and was discharged on the ninth postoperative day.

Comment. This asymptomatic presentation of a right cardiophrenic mass contiguous with the heart border is the more "typical" appearance of a pericardial cyst or diverticulum.

Case 11. This was the first hospital admission of a 40 year old male who entered following chest roentgenography which showed a mass in

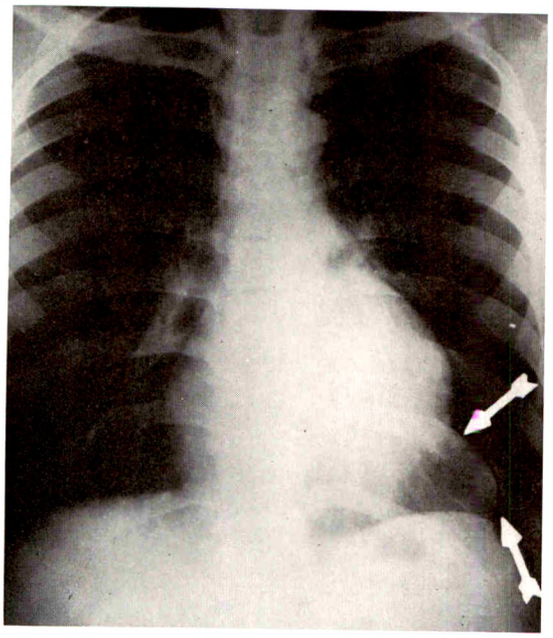


FIG. 3. Case II. Frontal chest roentgenogram shows a left cardiophrenic mass which seems to lift the left heart border slightly upward.

the lower left hemithorax. Physical examination was unremarkable.

A frontal chest roentgenogram demonstrated a left cardiophrenic mass which seemed to lift the left heart border slightly upward (Fig. 3).

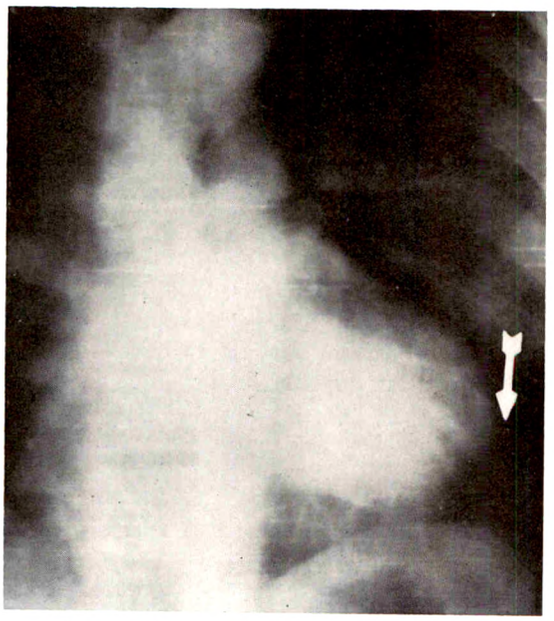


FIG. 4. Case II. Angiocardiogram fails to reveal cardiac or aortic involvement.

Angiocardiography failed to reveal any chamber involvement (Fig. 4).

Thoracotomy was performed and a pericardial cyst was removed.

Comment. Occasionally, slight variation in heart position will occur as a result of a pericardial cyst or diverticulum.

CASE III. This was the third hospital admission of a 60 year old female with the history of rheumatic heart disease since childhood. She was admitted at this time for an elective replacement of the aortic and mitral valves.

The patient had been asymptomatic until 1956. At that time, shortness of breath brought her to the hospital. She was digitalized and discharged well compensated. She had been followed as an out patient with the diagnosis of rheumatic heart disease with aortic insufficiency, aortic stenosis, mitral insufficiency and mitral stenosis. Chest examination since 1956 showed an enlarged heart.

Physical examination revealed findings of severe mitral and aortic valvular disease.

Chest roentgenograms in 1956 demonstrated a large anterior right paracardiac density which resembled a pericardial cyst or diverticulum (Fig. 5 and 6). At that time, considerable calcification of the left atrium was noted. Also,

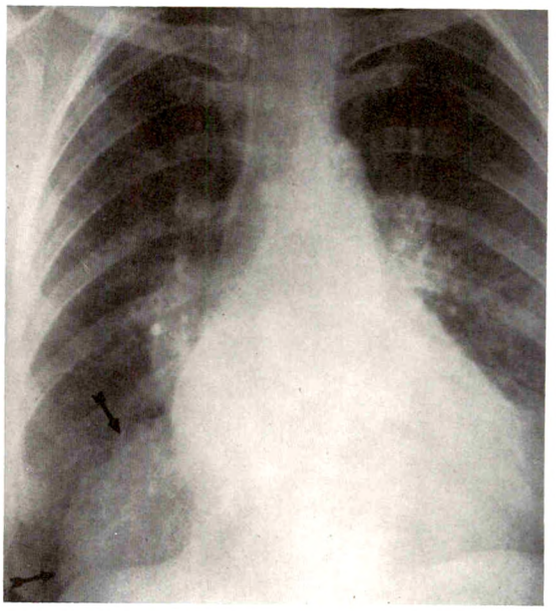


FIG. 5. Case III. Frontal chest roentgenogram 5 years prior to admission demonstrates a large heart with rheumatic configuration. A right paracardiac mass is noted. The left atrial wall is markedly calcified.

mitral valvular calcification was seen. Subsequent chest studies in 1962 and 1965 showed the density to have disappeared (Fig. 7). At that time, it was postulated that this was not a pericardial cyst but rather a pericardial diverticulum which emptied itself into the pericardial sac.

The patient was prepared for cardiac surgery and replacement of the mitral and aortic valves was performed. At this time a pericardial diverticulum was removed.

Comment. The ability to change size rapidly or to disappear completely is characteristic of a pericardial diverticulum.

Case IV. This was the first hospital admission of a 51 year old Puerto Rican male who entered with the chief complaint of left flank and back pain.

The patient was well until approximately 2 weeks prior to admission when he experienced left sided pain just under the lateral rib cage. This was mild but persistent until 1 day prior to admission when the pain became more severe. Associated with the pain was mild shortness of breath and two pillow orthopnea for the preceding 2 weeks.

On physical examination, positive findings were present in the chest. On the right side, wheezes and rhonchi were heard. On the left side, breath sounds were absent to the level of the mid-scapula. There was dullness to percussion on the left to the margin of the scapula.

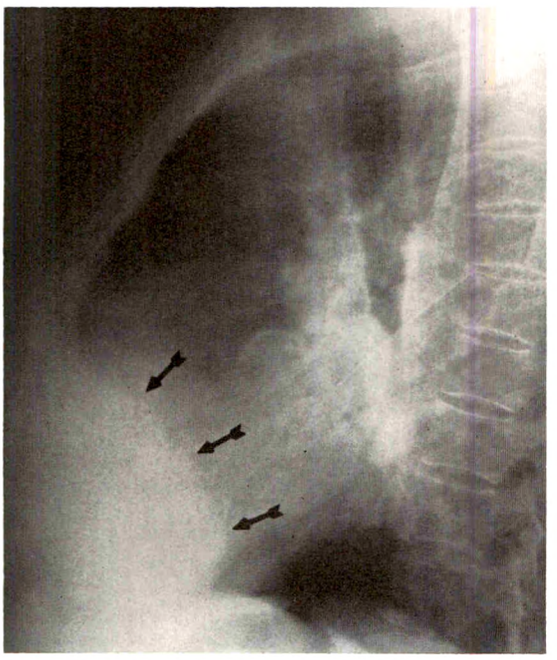


Fig. 6. Case III. Lateral roentgenogram shows the mass in the anterior mediastinum. Left atrial calcification is again noted.

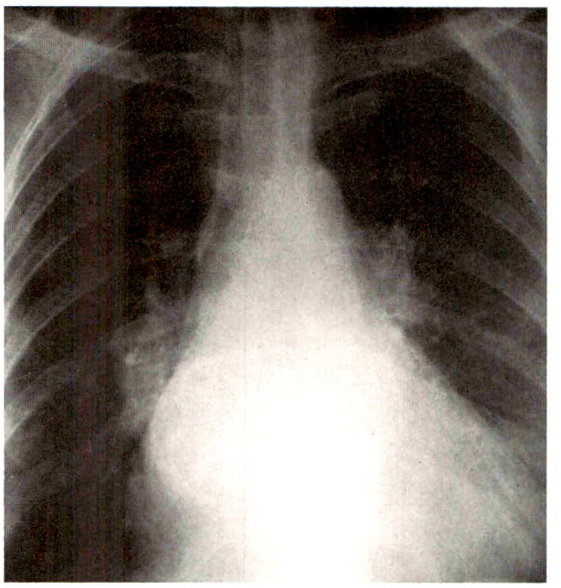


Fig. 7. Case III. Frontal roentgenogram on the present admission, 5 years following the first chest roentgenogram, again demonstrates left atrial wall calcification. At this time, the lower right paracardiac mass had disappeared. A right pericardial diverticulum was suspected with spontaneous emptying.

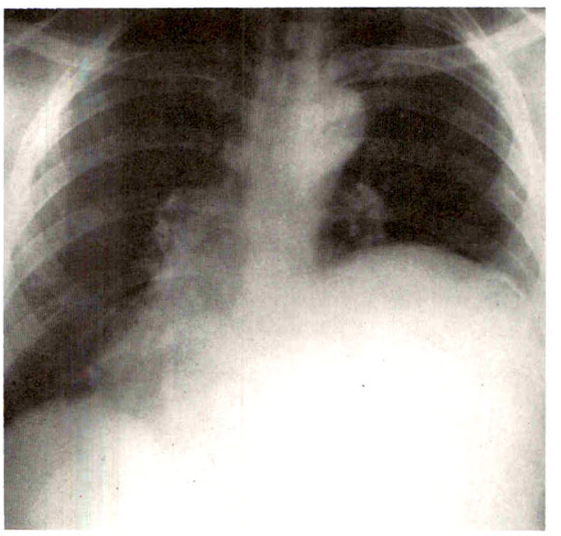


Fig. 8. Case IV. Frontal chest roentgenogram demonstrates a large mass blending with the left hemidiaphragm and displacing the heart to the right.

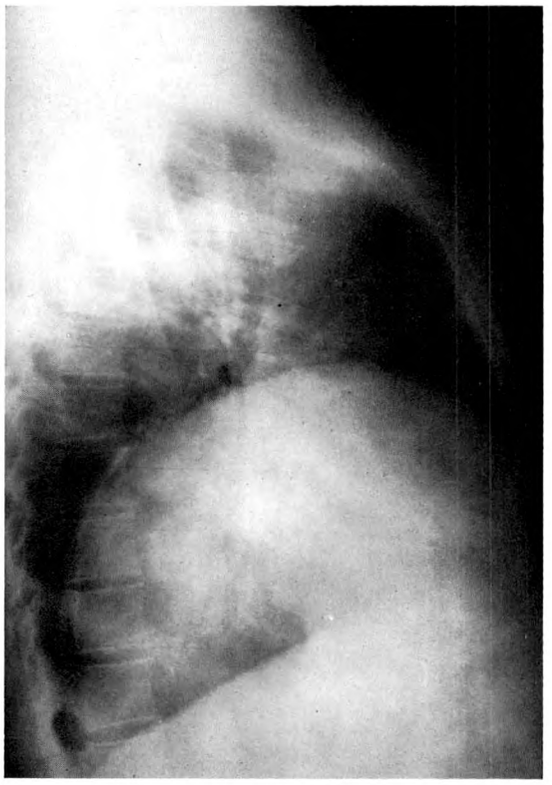


FIG. 9. Case IV. Lateral chest roentgenogram shows the density to span the entire anterior posterior diameter of the thorax.

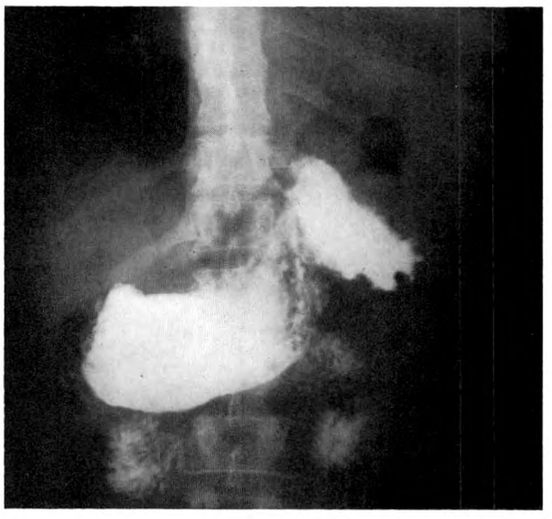


FIG. 10. Case IV. Gastrointestinal study reveals displacement of the stomach downward and to the right.

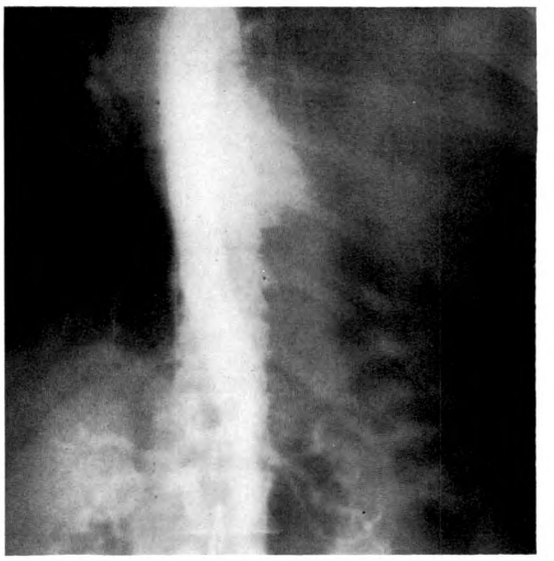


FIG. 11. Case IV. An intravenous aortogram shows a large soft tissue mass in the mid-trunk area obscuring the left diaphragm outline. The aorta appears to be displaced toward the right by the mass.

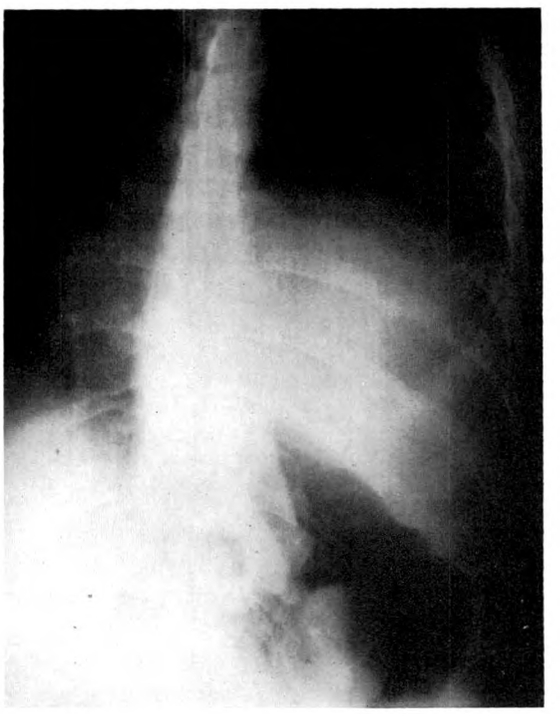


FIG. 12. Case IV. Pneumoperitoneum was performed to establish the location of the mass. Frontal roentgenogram defines the lower border of the mass to be in the chest.



Fig. 13. Case IV. Lateral roentgenogram showed the mass to be in the chest. No gas is seen to pass above the lower limits of the density.

Laboratory work-up was normal.

Roentgenographic examination of the chest revealed a large mass blending with the left hemidiaphragm (Fig. 8 and 9). The heart was displaced to the right. An intravenous pyelogram showed the left kidney to be depressed by the mass. Gastrointestinal series showed displacement of the stomach downward and to the right (Fig. 10). An intravenous aortogram demonstrated a large avascular soft tissue mass in the mid trunk area associated with the left diaphragm border (Fig. 11). It was not clear whether the mass was principally in the chest or the abdomen.

Pneumoperitoneum showed the mass to be in the left chest and resting upon the left hemidiaphragm (Fig. 12 and 13).

On the completion of the patient's diagnostic evaluation, it was felt that a large tumor was present in the left hemithorax. Exploratory thoracotomy was performed and a large pericardial cyst which contained 2,800 cc. of fluid was removed. The postoperative course was uncomplicated and the patient was discharged in excellent condition.

Comment. Pericardial cysts are only rarely symptomatic. In this case, the unusual size of the cyst produced symptoms as indicated above.

SUMMARY

The differential diagnosis of pericardial diverticulum or cyst is a broad one. Its importance stems from the more malignant lesions that it may mimic. A change in size and shape, or disappearance of the mass will often mean pericardial diverticulum. Both pericardial cyst and diverticulum tend to blend with the cardiac contour. The picture can vary considerably, however, thus leading most often to thoracotomy.

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MALNUTRITION WITH MICROCARDIA*

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A SMALL cardiac silhouette has many clinical and radiologic implications. Normally, an asthenic build may exhibit roentgenographic microcardia.[16] Clinical states such as acute dehydration,[15] adrenal insufficiency,[13] obstructive emphysema, and nephrosis[3] may accompany a small cardiac silhouette. The pathophysiologic explanation is deficient or unexplored in many instances while cardiac atrophy as a contributing factor is for the most part overlooked. Observing changes in cardiac size on serial chest roentgenograms of patients exhibiting extreme progressive weight loss stimulated investigation in this unexplored area. The resultant study adds cardiac atrophy to the list of causalities of roentgenographic microcardia.

MATERIAL AND METHODS

The antemortem diagnosis of pathologic microcardia depends upon the roentgenographic evaluation of the cardiac silhouette. Occasionally, the electrocardiogram suggests the presence of cardiac atrophy, but in most instances the changes are nonspecific.[11] With this in mind, a pathologic, clinical and roentgenologic review was carried out on 24 patients who exhibited microcardia at postmortem examination. Eighteen patients were selected in a retrospective manner with roentgenograms reviewed subsequent to the pathologic diagnosis, while 6 were investigated because of roentgenographically evident microcardia prior to postmortem examination. Eleven males and 13 females with an average age of 56 years were studied. Periods of weight loss ranged from 3 months to 8 years (average 16 months). The extent of weight loss varied from 18 pounds to 124 pounds (average 50 pounds). Cardiothoracic ratios were determined on 21 patients. Chest roentgenograms prior to weight loss were available in 12 instances, providing serial observations of the changing cardiac size. Although blood volume studies employing dilution principles were not available, periodic hemoglobin, hematocrit and urinary specific gravity determinations were used in an attempt to evaluate the state of hydration and stability of blood volume.

PATHOLOGIC OBSERVATIONS

The diagnosis of pathologic microcardia (atrophy) was based on the criteria listed in Table 1.[8,10] The autopsy protocols classified 17 hearts as brown atrophy, 4 as simple atrophy (a small heart without excessive lipochrome pigmentation) while 3 were unclassified. The cardiac weights ranged from 160 to 280 gm. (normal range 250 to 350 gm.).[1] Fragmentation of muscle fibers, absent mitotic figures and increased lipochrome pigmentation of the sarcoplasm were the most persistent and reliable microscopic findings (Fig. 1, *A* and *B*). The gross pathologic study, including ventricular wall measurements, revealed a marked decrease in the cardiac chamber size with a relatively

TABLE I

CRITERIA FOR PATHOLOGIC CARDIAC ATROPHY

1) Decreased heart weight relative to total body weight
2) Excessive lipochrome pigmentation of cardiac muscle fibers
3) Serous atrophy of the subepicardial fat
4) Increase in the nuclear fiber ratio
5) Decreased muscle fiber size
6) Fragmentation of muscle fibers
7) Absence of normal mitoses

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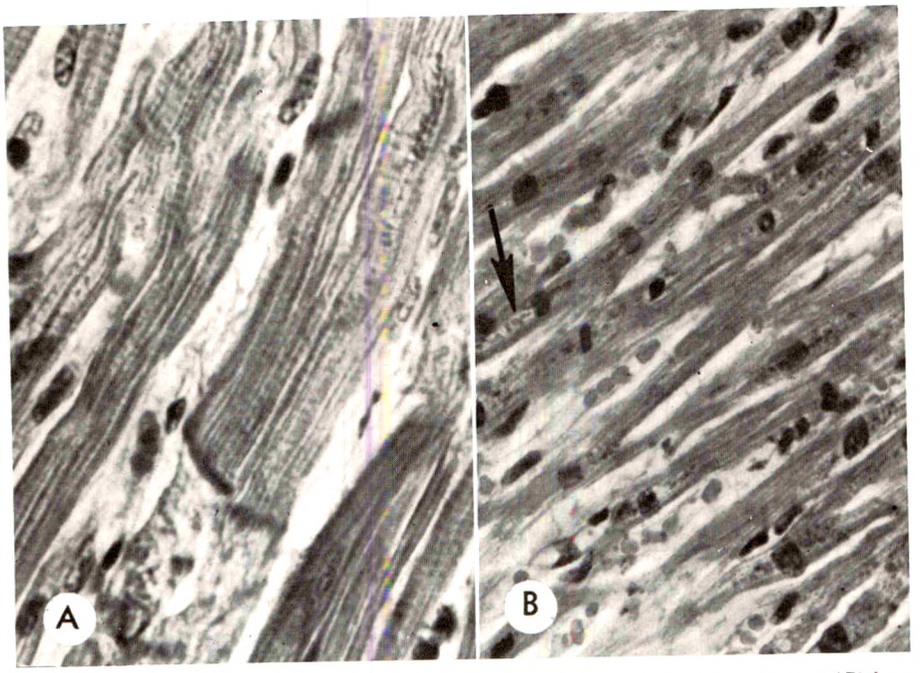


Fig. 1. Photomicrographs (both final magnification ×400) of (*A*) normal heart muscle and (*B*) brown atrophy of the myocardium. Although the nuclear size is similar in both, the number of fibers per unit area is increased in the atrophic myocardium. Note also the increased nuclear-fiber ratio, lipochrome pigment at the nuclear poles (arrow), and fragmentation of the muscle fibers.

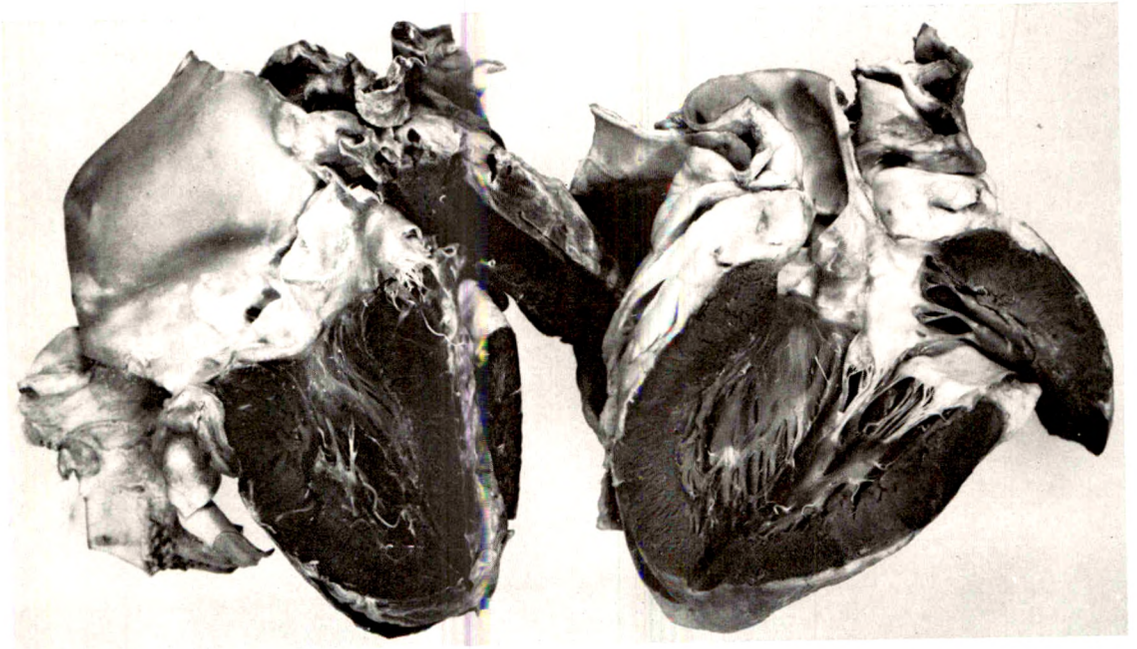


Fig. 2. Gross pathology: Normal heart on the right (wt. 288 gm.); brown atrophy on the left (wt. 220 gm.). Note dark discoloration of myocardium and the greater reduction of chamber size relative to myocardial thickness represented by the atrophic heart on the left.

TABLE II

PRIMARY PREDISPOSING FACTORS TO MALNUTRITION

Disease Process	No. of Cases	Disease Process	No. of Cases
1) *Carcinomatosis*	*16*	2) *Lymphoma*	*3*
Breast	4	Hodgkin's disease	2
Stomach	4	Lymphosarcoma	1
Cervix	3	3) *Ulcerative colitis*	*2*
Lung	2	4) *Scleroderma*	*1*
Pancreas	2	5) *Anorexia nervosa*	*1*
Rectum	1	6) *Hepatoma*	*1*

less corresponding decrease in the ventricular wall thickness (Fig. 2). This discrepancy has been noted by others[7] and is considered a contributing factor in the development of cardiac failure with aggressive intravenous infusion in patients exhibiting malnutrition and microcardia.

ETIOLOGY

Although malnutrition was the underlying etiologic factor in all cases, a more meaningful appraisal of the contributing factors unfolded when the primary disease processes were subdivided into secondary contributing factors (Table II and III). The complexity of factors predisposing to generalized body atrophy and, in turn, cardiac atrophy was exemplified. The assumption that metabolic demands are further intensified by multiple primary malignancies prompted the inclusion of this factor in the secondary group.

ROENTGENOGRAPHIC FINDINGS

Chest roentgenograms were available on 21 patients. Fifteen patients had serial studies at varying time intervals, and all but 3 demonstrated a significant reduction in the size of the cardiac silhouette (Fig. 3 through 5). In the latter group, 1 patient failed to demonstrate a statistically satisfactory reduction in the cardiothoracic ratio, while massive pericardial metastases and pericardial effusion explained the unaltered cardiothoracic ratios in the remaining 2 cases. Of the 6 patients where single chest roentgenograms were available and obtained shortly before postmortem examination, all exhibited cardiothoracic ratios below or within the low range of normal (Fig. 6). In view of the average patient weight (145 pounds), average age (56 years) and constant anemic states, cardiothoracic ratios falling below the adult mean

TABLE III

SECONDARY PREDISPOSING FACTORS TO MALNUTRITION (14 OF 24 CASES)

Secondary Factor	No. of Cases	Primary Factor	Specific Complication
Multiple primary malignancies	5	Carcinomatosis (3)	Stomach and breast Cervix and pancreas Pancreas and maxilla
		Hepatoma	Aplastic anemia
		Anorexia nervosa	Hypopharyngeal and rectal carcinoma
Multiple operative procedures	2	Carcinomatosis (cervix) Carcinomatosis (lung)	Small bowel obstruction Multiple abdominal operations
Total gastrectomy	2	Carcinoma stomach (2)	—
Secondary intestinal malabsorption	2	Ulcerative colitis Scleroderma	—
Chronic dysphagia	2	Carcinomatosis (breast) Hodgkin's Stage III	Metastatic esophageal stricture Uncontrolled neck mass
Chronic anorexia	1	Carcinomatosis (lung)	Severe obstructive emphysema

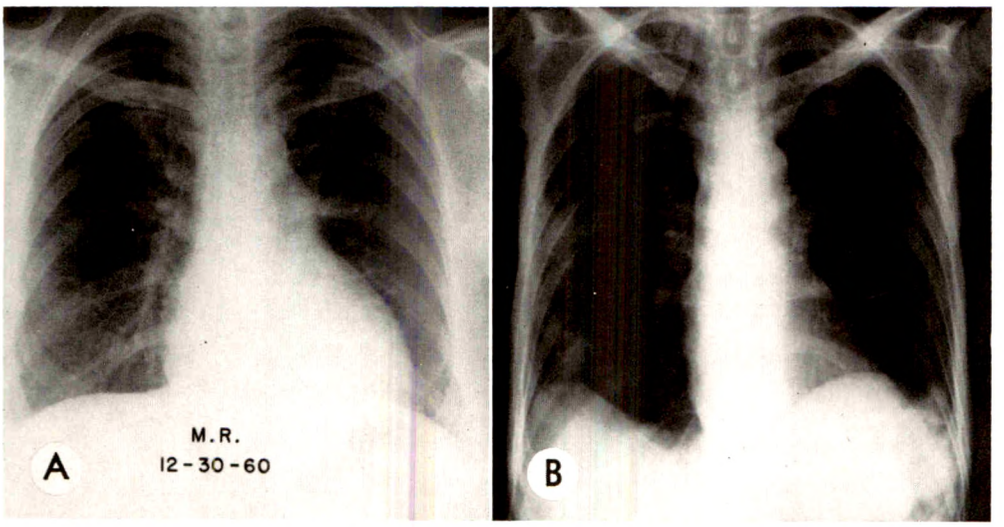


FIG. 3. (*A*) Roentgenogram obtained prior to weight loss (original weight 189 lb.). Carcinoma of the stomach with generalized metastasis led to a 124 lb. weight loss in 12 months with (*B*) resultant chest roentgenogram.

were considered significant. Excessive soft tissue wasting, progressive diminution of the pericardial fat pad, and increased radiolucency of the lung were the most significant associated roentgenologic findings (Fig. 7 *A*, *B* and *C*).

STATISTICAL ANALYSIS

Various data were subjected to statistical analysis, utilizing the least square method. The observed correlation coefficient between postmortem heart weight and final cardiothoracic ratios was statistically in-

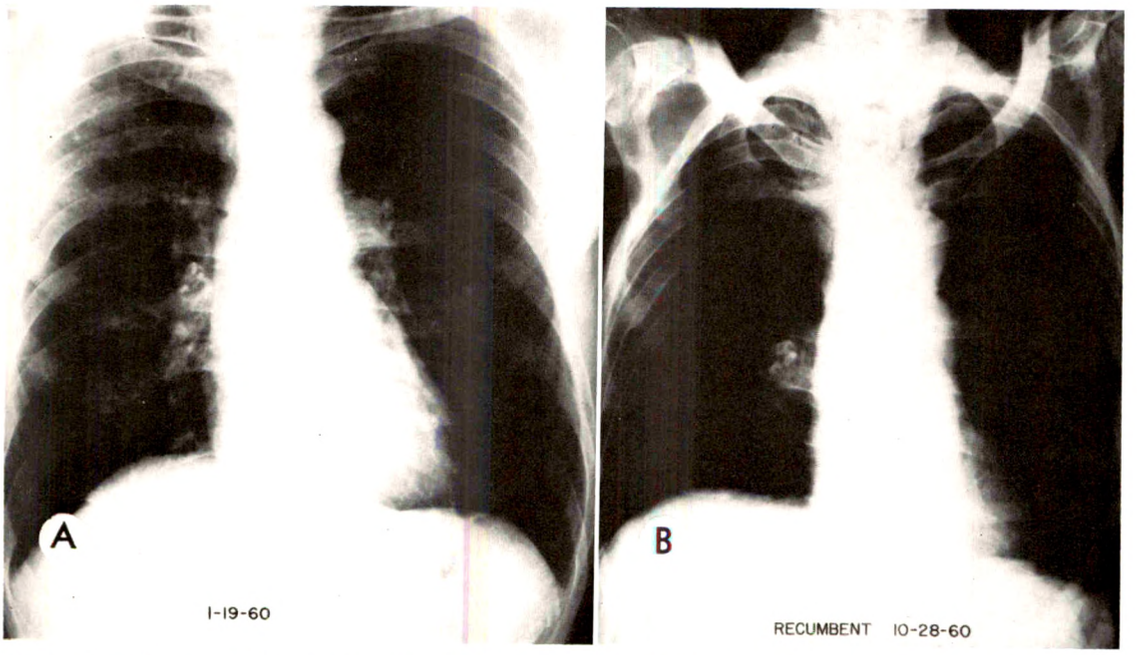


FIG. 4. Sixty-four year old male who developed severe malnutrition following total gastrectomy for adenocarcinoma of the stomach. A 40 lb. weight loss was experienced over a 14 month period. (*A* and *B*) Roentgenograms represent a 9 month interval with resultant soft tissue wasting and a reduction in cardiac size; brown atrophy of the heart was found at postmortem examination (wt. 220 gm.).

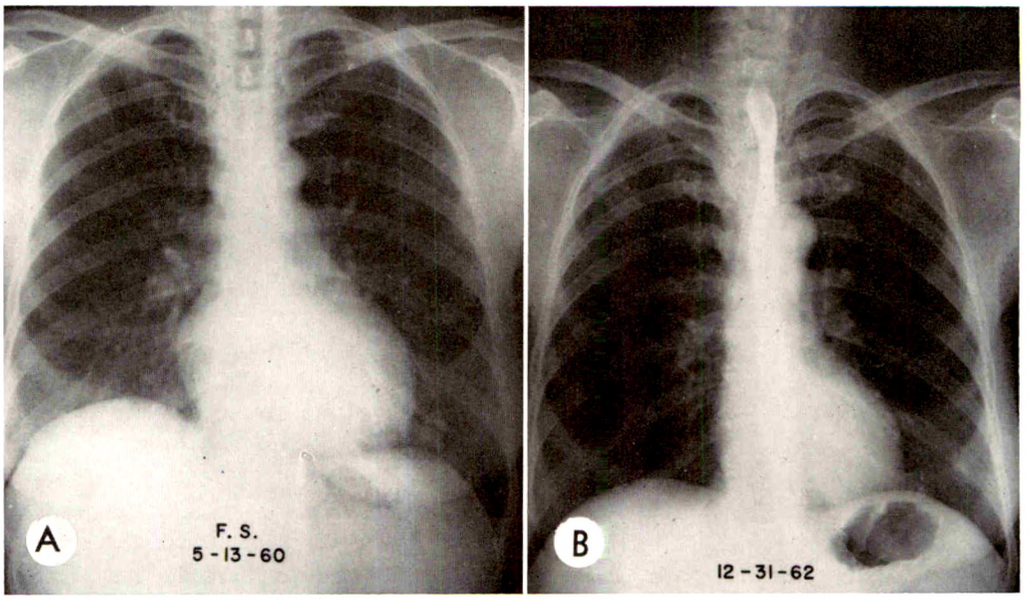


Fig. 5. (*A* and *B*) Serial chest roentgenograms in a case of Stage III carcinoma of the cervix with subsequent generalized metastasis which led to a 35 lb. weight loss over a 19 month period.

significant and indicated a lack of association (Fig. 6). The failure of correlation between these two variables accentuates the importance of blood volume, phase of respiration, phase of cardiac cycle and degree of peripheral vascular resistance in determining the size of a cardiac silhouette.

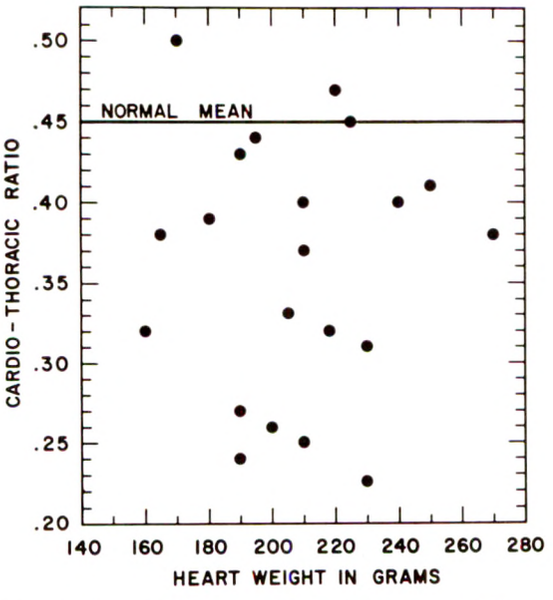


Fig. 6. Scattergram relating cardiothoracic ratio to postmortem heart weight. The two variables do not statistically correlate (correlation coefficient .550). Other factors obviously contribute to the final cardiothoracic ratio in malnourished states.

DISCUSSION

During a brief period following the second World War, attention was focused on the effects of starvation upon the cardiovascular system.[4,5,12,19] The rehabilitation of prisoners who suffered from starvation and inanition emphasized the reversibility of cardiac atrophy and its associated sequelae. Rarely was roentgenologic correlation made[7] and studies incorporating variables influencing cardiac size were often omitted.

Diminished blood volume and mechanical compression by emphysematous lungs are well known causes of roentgenographic microcardia.[9,13,21] However, any disease process accompanied by marked inanition and weight loss may give rise to cardiac atrophy and, in turn, influence the size of the cardiac silhouette. With this in mind, caution must be employed in using the size of the cardiac silhouette as a guide in evaluating optimal replacement therapy in Addison's disease[9] or any other hypovolemic state where inanition is part of the clinical picture. Cardiac decompensation develop-

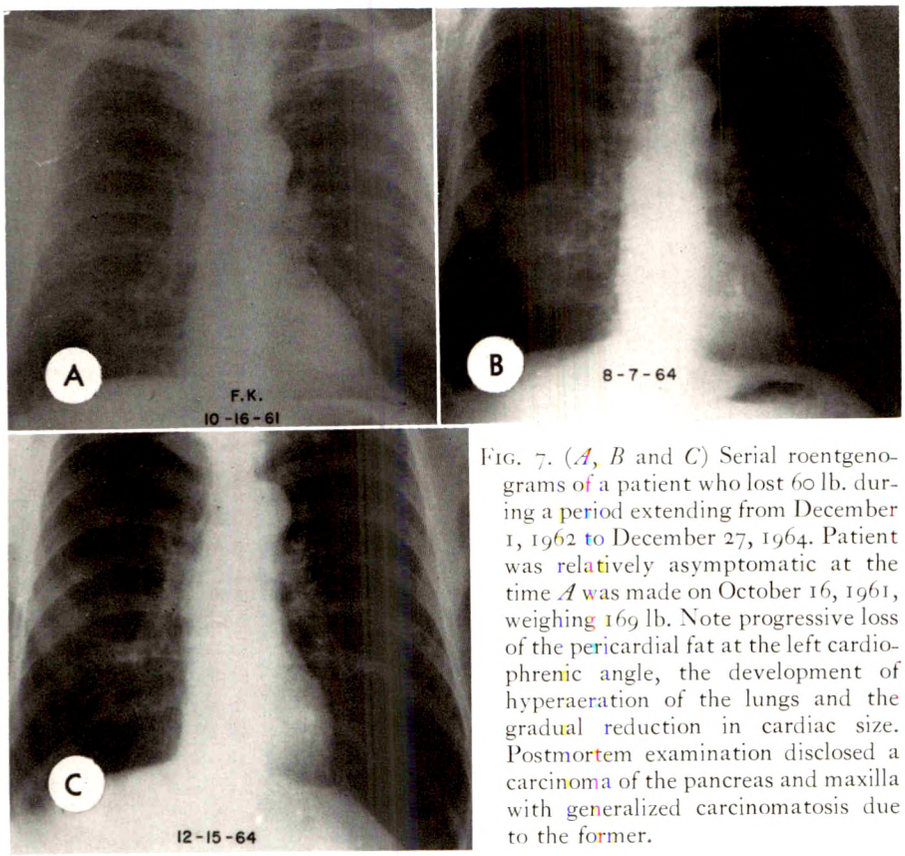


FIG. 7. (*A*, *B* and *C*) Serial roentgenograms of a patient who lost 60 lb. during a period extending from December 1, 1962 to December 27, 1964. Patient was relatively asymptomatic at the time *A* was made on October 16, 1961, weighing 169 lb. Note progressive loss of the pericardial fat at the left cardiophrenic angle, the development of hyperaeration of the lungs and the gradual reduction in cardiac size. Postmortem examination disclosed a carcinoma of the pancreas and maxilla with generalized carcinomatosis due to the former.

ing with an overdose of desoxycorticosterone[6] may also be related to the reduced cardiac capacity found in association with cardiac atrophy. Overloading the circulating blood volume by intravenous infusion with resultant cardiac decompensation occurred in 2 patients in this study. Other than extreme cardiac atrophy, the hearts were normal at postmortem examination. Excessive myocardial fibrosis, which not infrequently accompanies brown atrophy of the heart, was also found. Cardiac fibrosis causes a reduction in the systolic stroke volume[13] and further contributes to the development of cardiac failure, especially in hypervolemic states.

The contribution of hypovolemia to roentgenographic microcardia was difficult to assess with certainty in this study. The maintenance of stable hematocrit values coincident with chest roentgenogram obtained prior and subsequent to weight loss suggested stable plasma volumes.[21] Furthermore, the occurrence of hypervolemia in chronic malnourished states is the rule rather than the exception according to many authors.[2,14,18] This is particularly true when total blood volume is expressed as a per cent of actual body weight.[17] Acute dehydration was often part of the clinical picture in many patients in this study. However, serum electrolyte and urinary specific gravity determinations failed to correlate its presence when chest roentgenograms were obtained. Failure to correlate postmortem heart weights and final cardiothoracic ratios reflected the extreme difficulty in attempting to attribute any one factor as paramount to the development of roentgenographic microcardia.

Evidence of soft tissue wasting and progressive diminution of pericardial fat provides further support in attempting to relate roentgenographic microcardia to pathologic cardiac atrophy. Marked weight loss should be part of the clinical picture.

Attributing a specific cause to the development of malnutrition in the chronically ill patient is as complex as attempting to assign a single factor responsible for roentgenographic microcardia.

SUMMARY

Roentgenographic microcardia or a shrinking cardiac silhouette observed on serial chest roentgenograms was associated with pathologic cardiac atrophy in 18 of 21 patients. Microscopic and gross pathologic study classified 17 hearts as brown atrophy, 4 as simple atrophy, with 3 specimens unclassified. The relationship of malnutrition and chronic illness with complicating factors was reviewed. Cardiac decompensation as a sequela of cardiac atrophy during hypervolemic states was observed in 2 patients. Cardiac atrophy was added to the list of causalities of roentgenographic microcardia.

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VOL. 99, NO. 3

UNILATERAL BULLOUS EMPHYSEMA*

ANGIOCARDIOGRAPHIC STUDY OF TWO CASES

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ORDINARILY, unilateral bullous emphysema is a threat to health because of the danger of rupture of a bulla, creation of a tension pneumothorax, and, thereby, serious impairment of the function of the contralateral lung, especially when there is associated infection.[1–7] That such a course is not always inevitable is underscored by the report of 2 patients, the first a 9 year old girl who apparently tolerated unilateral bullous disease of the right lung for many years, and the other, a 53 year old man who had had extensive bullous emphysema of the left lung for over 15 years. In addition to conventional roentgenograms of the chest, angiocardiography was utilized to better evaluate the state of the pulmonary circulation in the disease,[1,2,3,7] and is another reason for this report.

REPORT OF CASES

CASE I. *Bullous emphysema of the right lung.* A 9 year old girl (N.Y.H. No. 310035) was admitted on October 20, 1941, with the complaint of a "collapsed lung" of 6 months' duration. She was the product of a normal, full term, spontaneous delivery. Weight at birth was 10 pounds, 3 ounces. Weight gain had been slow for the first 9 months. Six months prior to admission, the patient developed a cold, which was associated with a nonproductive dry cough. Because of persistence of the cough, her doctor made a roentgenogram of the chest. This showed a "collapsed lung," and the patient was put to bed. Another roentgenogram of the chest made 2 weeks later was unchanged. A consultant also made roentgenograms of the chest, and again prescribed bed rest. During the following summer, the patient lived in Maine, where the cough disappeared and she gained 14 pounds. On her return, because the roentgenogram of the chest was unchanged, hospitalization was advised.

Physical examination revealed a thin, alert girl of 9 years of age, not appearing ill. The thorax was asthenic; she had a moderate funnel chest without asymmetry. The lungs had good expansion with slight hyperresonance of the right side. The breath sounds were also diminished and there were no rales. Roentgenogram of the chest showed bullous emphysema of the right lung with mediastinal herniation and deviation of the trachea and heart into the left hemithorax. There was also a large pectus excavatum (Fig. 1*A*). Angiocardiography on October 31, 1941, showed a huge bulla involving almost the entire right lung and causing severe mediastinal herniation. The heart was rotated into the left hemithorax and only meager pulmonary arterial and venous circulation of the right lung was evident, whereas the left pulmonary arterial and venous circulations were intact (Fig. 1, *B* and *C*).

During her hospital course, the child was afebrile and without cough. On November 10, 1941, 400 cc. of air was aspirated from the right chest without causing change in pressure. Three days later, thoracentesis was repeated, the needle being inserted into the right thorax just above the sixth rib. This time, 520 cc. of air was removed. Following this, a roentgenogram of the chest again showed unchanged bullous emphysema of the right lung. She was discharged on December 7, 1941.

Communication revealed that 2½ years later, she had been admitted to another hospital where a funnel chest, multiple cysts of the right lung, and partial pneumothorax, apparently attributed to a ruptured apical cyst, were found. An operation to correct the pectus excavatum was performed in 3 stages with straightening of the sternal deformity but without treatment of the bullous emphysema. Since then, follow-up study has not been possible.

CASE II. *Bullous emphysema of the left lung.* A 53 year old man (N.Y.H. No. 1051151) was admitted on May 12, 1966, with a chief com-

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† Recipient of Career Scientist Award of the Health Research Council of the City of New York under contract U-1648 and I-258.

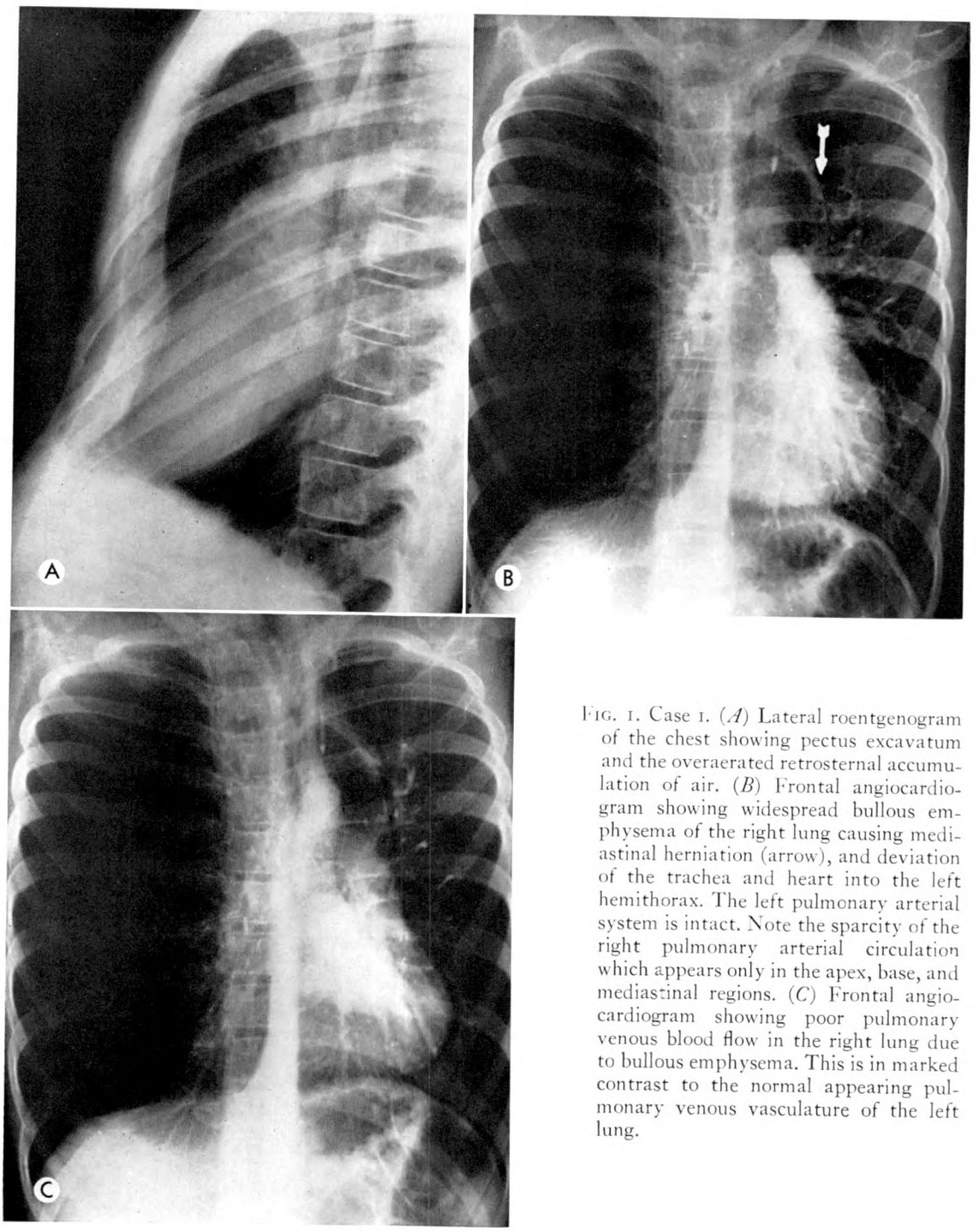


Fig. 1. Case 1. (*A*) Lateral roentgenogram of the chest showing pectus excavatum and the overaerated retrosternal accumulation of air. (*B*) Frontal angiocardiogram showing widespread bullous emphysema of the right lung causing mediastinal herniation (arrow), and deviation of the trachea and heart into the left hemithorax. The left pulmonary arterial system is intact. Note the sparcity of the right pulmonary arterial circulation which appears only in the apex, base, and mediastinal regions. (*C*) Frontal angiocardiogram showing poor pulmonary venous blood flow in the right lung due to bullous emphysema. This is in marked contrast to the normal appearing pulmonary venous vasculature of the left lung.

plaint of pain in the chest. He had had "double pneumonia" at the age of 8 years and remembered always being dyspneic on exertion. In 1940, he had his first episode of chest pain and was treated by strapping of the chest. In 1943, he was refused induction into the military service by the draft board because of large left lung cysts noted on roentgenograms of the chest. For several years prior to admission, he had increasing dyspnea and 1 pillow orthopnea.

Because of these symptoms, he was examined and a roentgenogram of the chest was made in January 1951. He was advised to enter the hospital for further studies but refused. For 1 year prior to admission, he had multiple chest colds, a productive cough, but no hemoptysis. Three weeks prior to entry, he noted increased left chest pain, thoracic pressure, and discomfort when lying on the left side. Physical examination showed absent fremitus and breath sounds and tympany over the left hemithorax. The right lung was clear. There were no cardiac murmurs, the pulse was 80, and the blood pressure was 140/90 mm. Hg. The electrocardiogram was normal. Conventional roentgenograms of the chest showed huge bullae of the entire left hemithorax, attached by a broad band to the left lateral chest wall and with only moderate displacement of the heart, mediastinum, and lung (Fig. 2, *A* and *B*). Except for slightly increased right-sided displacement, this was little changed from the roentgenogram made 15 years earlier.

An intravenous angiocardiogram made on May 13, 1966, demonstrated some lateral displacement of the superior vena cava to the right of the sternum. The main pulmonary artery and right branch were normal, but the left pulmonary artery was seen only on "end"; the branches from it were present only at the hilus. The left lung contained a huge cyst, apparently attached laterally to the left chest wall. The right pulmonary circulation was normal (Fig. 2, *C* and *D*). On May 13, 1966, under local anesthesia, a chest tube was placed into the left pleural space. Brisk bubbling resulted in the underwater seal, which persisted at an unchanged rate. Because of the continuous flow without expansion of the lung parenchyma, it became obvious that the chest tube had been inserted into an emphysematous bleb. Accordingly, the tube was removed on the first postoperative day. Further surgery seemed unnecessary because the chest pain and pressure were alleviated. He continued to be well and was discharged on May 19, 1966. Dyspnea on exertion has continued, but he has been able to resume his regular work as a shoe salesman.

DISCUSSION

Conventional roentgenography is usually sufficient for the diagnosis of bullous emphysema, especially when the disease is extensive and unilateral (Fig. 2, *A* and *B*). Angiocardiography by opacifying the pulmonary circulation enhances the diagnosis of bullous emphysema by demonstrating the extent of the pulmonary vascular involvement (Fig. 1, *B* and *C*; and Fig. 2, *C* and *D*), and has been found useful for selection of the case suitable for surgery.[1,3]

The 2 cases reported above—the first a child of 9 years of age and the other a 53 year old man—illustrate that extensive, unilateral bullous emphysema may exist for many years and yet cause few complaints and even allow the patient to work (Case 11). Bullous emphysema probably began early in life in the first patient, but diagnosis was delayed until she was 9 years, when a chance roentgenogram of the chest, made because of a cough, showed widespread disease of the right lung. In Case 11, the patient was asymptomatic and bullous emphysema was discovered only after a routine roentgenogram was made prior to induction into the military service. Even following diagnosis, he was able to do his regular work for 7 years, until increasing dyspnea and cough led him to request examination. At that time, he had extensive bullous emphysema of the left lung but with only slight shift of the mediastinum and heart into the right hemithorax. Despite dyspnea, he was gainfully employed for the next 15 years. Finally, because of increased chest pain, a left pneumothorax complicating the bullous emphysema was suspected, and tube drainage of the left hemithorax was instituted. When the roentgenogram of 15 years earlier was reviewed, it was evident that the drainage tube was located in a bullous rather than in a pneumothorax, and so air suction was quickly abandoned. Thus, pleural and pulmonary infections were avoided. The relief of pain that followed was probably due to the enforced bed rest rather than to the effects of the surgery. In any event, the patient improved rapidly and was able to resume his regular work, albeit still symptomatic, thus illustrating that extensive uni-

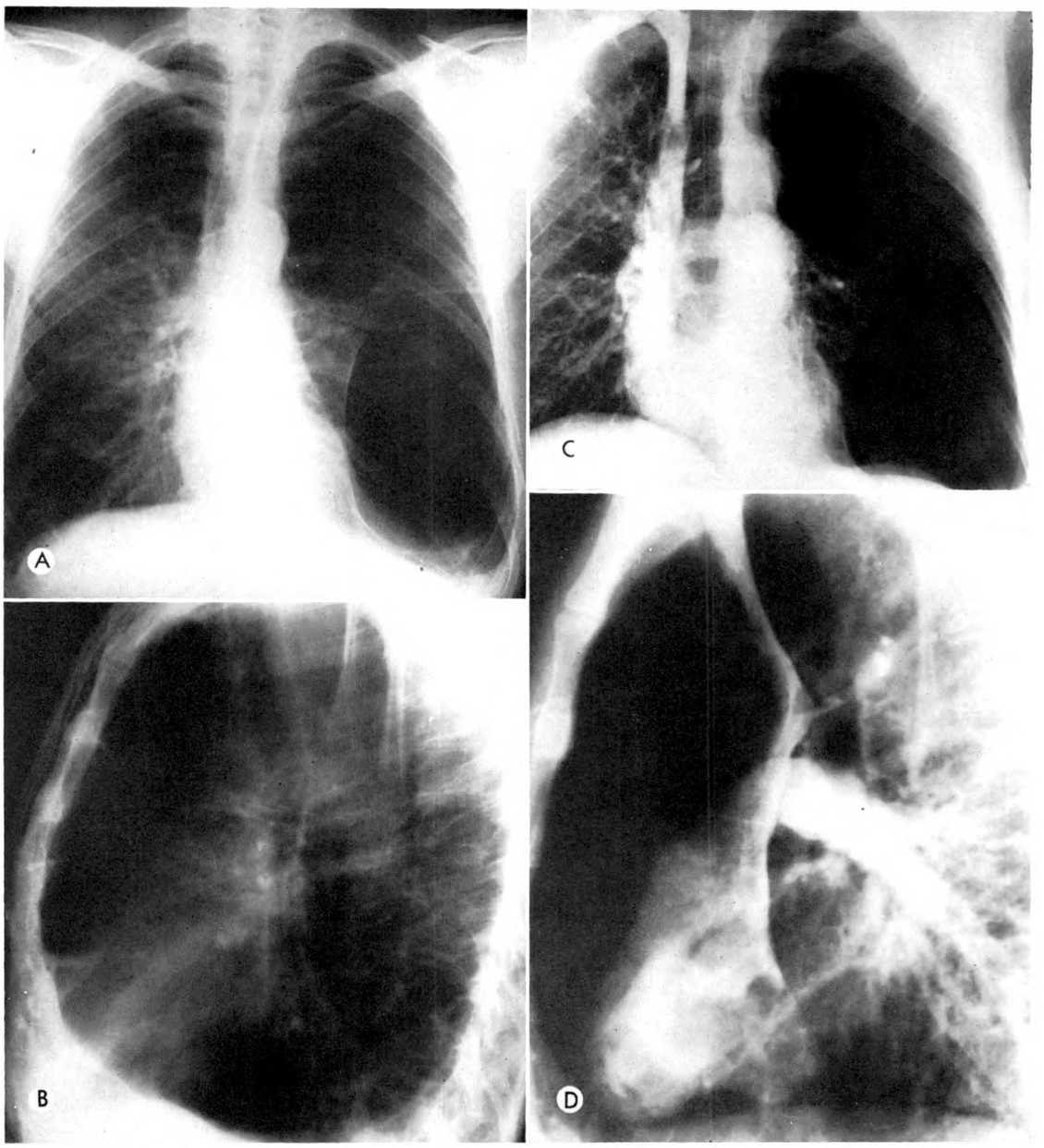


Fig. 2. Case II. (*A*) Frontal teleroentgenogram of the chest showing bullous emphysema of the entire left lung but with only mild deviation of the trachea, mediastinum, and heart. Note adhesion of the left-sided bulla to lateral chest wall. (*B*) Lateral view of chest showing voluminous thorax with marked overaeration of the lung in the retrosternal area. (*C*) Frontal angiocardiogram showing only minimal left hilar pulmonary arterial blood flow in the portion of the lung that is attached to the left chest wall. The right lung appears to be intact and there is only mild deviation of the cardiovascular structures towards the right hemithorax. (*D*) Lateral angiocardiogram (biplane view of *C*) shows the absent vasculature of the left lung. Note the hyperaerated retrosternal area due to the bullous right lung.

lateral bullous emphysema may be relatively well tolerated for many years.

SUMMARY AND CONCLUSIONS

Two patients, the first a 9 year old girl with extensive bullous emphysema of the right lung and the other a 53 year old man with bullous emphysema of the left lung, both studied angiocardiographically, are reported in order to illustrate that such widespread disease is consistent with relative well-being over many years. Although the first case was lost to follow-up at the end of 3 years, the older patient was seen regularly over a period of 15 years, and remained fairly well despite increasing dyspnea and chest pain. Exacerbation of chest pain was attributed to pneumothorax and tube drainage of the left hemithorax was instituted. When it was realized that a bulla rather than pneumothorax was being aspirated, air suction was quickly abandoned before pleural infection occurred. The patient improved and was able to resume his regular employment, thus emphasizing that excessive unilateral bullous emphysema may be well tolerated for many years. Surgical treatment of bullous emphysema should probably be reserved for those patients who become handicapped by rupture of bullae, tension pneumothorax, infection, disabling dyspnea, or severe compression of intact pulmonary tissues.[3] Angiocardiography in such instances is chiefly of value for demonstrating the state of the circulation in the contralateral and diseased lungs.

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A THIN-WALL DOUBLE CATHETER SYSTEM FOR TRANSTRACHEAL BRONCHOGRAPHY*

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THE convenience and safety of transtracheal bronchography have been well documented in the literature. The use of a catheter introduced transtracheally has been popularized recently, as it allows selective catheterization of the bronchi.[1,5] Hemley and Kanick[2] feel that the catheter technique is limited because instillation of the contrast medium is difficult due to its high viscosity. This problem has not been emphasized by those using relatively small bore catheters such as the red Ödman arterial catheter[4] and catheters that are passed through a needle.[6]

TECHNIQUES

It was felt by the author that a thin-wall catheter would allow a more adequate inner diameter while maintaining a satisfactory outer diameter. Steckel and Grillo[5] report the use of a thin-wall teflon catheter which appears to be relatively satisfactory; however, a double thin-wall catheter system made of radiopaque polyethylene has been devised that allows great flexibility in use and has attained good results. It is patterned after the catheters used for angiography by Riley *et al.*[3] and is introduced using the Seldinger technique with a 0.0315 inch guide wire.* The outer catheter, 30 cm. in length, has outer and inner diameters of 0.083 and 0.062 inch, while the inner catheter, 35 cm. long, has outer and inner diameters of 0.054 and 0.037 inch.†

The outer catheter is tapered to the inner catheter, both of which have been precurved (Fig. 1). If selective catheterization that necessitates an increase in the curve is desired, the inner catheter may be reinserted and the curve adjusted by varying the distance it protrudes from the outer catheter. The bronchus in question may be selectively catheterized with the inner catheter, over which the outer catheter is advanced. The inner catheter is then removed prior to the injection of the contrast medium. The system may be satisfactorily seen with image intensification fluoroscopy.

After suitable positioning of the outer catheter, a 16 gauge disposable needle is inserted, obviating the use of a stopcock. The entire system is thus easily made and completely disposable.

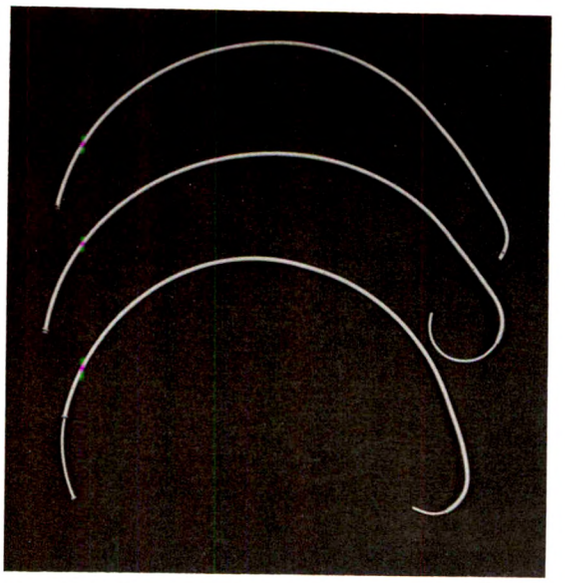


Fig. 1. Radiopaque thin-wall polyethylene catheter system. *Upper:* The outer catheter alone. *Middle and lower:* The double catheter system. The curvature may be diminished by partial withdrawal of the inner catheter.

* Catalog No. F-315-80. Cook, Inc., Bloomington, Indiana.
† Catalog No. RPX 062 and RPX 037. Becton, Dickinson and Co., Rutherford, New Jersey.

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The views expressed herein are those of the author and do not necessarily reflect the views of the United States Army or the Department of Defense.

SUMMARY

A new thin-wall double catheter system for transtracheal bronchography is described. It is easily made, allows great flexibility in use and is disposable.

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A COMPARATIVE STUDY OF ROENTGENOGRAPHIC TECHNIQUES FOR DETECTION OF CALCIUM PYROPHOSPHATE DIHYDRATE DEPOSITS (PSEUDOGOUT) IN HUMAN CARTILAGE*

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AN ARTICULAR syndrome often associated with distinctive roentgenologic features has recently been described. Zitnan *et al.*[12–15] utilized these features to define the condition, which they named "articular chondrocalcinosis." McCarty *et al.*,[3,5] using specific techniques to identify the microcrystalline calcium pyrophosphate dihydrate previously found in joint fluid,[4] named the condition "pseudogout" to emphasize the striking clinical and pathologic resemblance to classic gout. The disease is *defined* crystallographically, however, and not by the clinical features. The roentgenologic features of this peculiar affliction have been previously described.[6,7,14]

In this paper a comparative study of several roentgenographic techniques for detection of calcium pyrophosphate dihydrate crystal deposits in human cartilage is described. The determination of an optimum roentgenographic technique is vital because of its diagnostic importance and its potential usefulness in family and population studies. The recent description of 3 distinct types of crystal deposits in menisci from human cadavers[8] serves to emphasize the need for an optimum roentgenographic technique and careful roentgenologic interpretation.

METHODS AND MATERIALS

Stanton and Lightfoot[10,11] have recently reviewed the principles required to obtain roentgenograms of maximum resolution (detail) and contrast in relation to mammography. These same principles were applied in the present study. Four types of film: routine screen, medical no-screen, industrial AA and industrial M, were exposed as shown in Tables I and II. The hands and wrists, elbows, ankles, knees, and shoulders of 18 patients with "definite" pseudogout according to published criteria[6] were examined. Film types AA and M were simultaneously exposed, while medical no-screen film and routine screen film were separately exposed using the same projection but different factors.

The contrast of type M film is greatest, AA intermediate and no-screen least for any given kilovoltage exposure. The "speed" of these films is inversely related to contrast with no-screen fastest and type M slowest. All 3 are considerably slower than routine screen film. Contrast rises rapidly as peak kilovoltage is lowered. Visual contrast rises proportionately with the density of the roentgenogram. It is apparent, therefore, that a balance of film type, peak kilovoltage and milliampere-seconds is necessary to provide roentgenograms of maximum detail and contrast and maintain patient dose, anode heat and patient motion (blur) within acceptable limits.

Inherent infiltration only was used to ensure maximum contrast. Penumbra was reduced by using a 1 mm. focal spot and

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Table I

TECHNIQUE FOR ROUTINE SCREEN FILM (DUPONT CRONEX II)*

Joint	Time (sec.)	Kv. peak	Screen	Grid
Hand and Wrist	1/20	56	ultradetail	None
Elbow	1/20	70	ultradetail	None
Ankle	1/20	72	ultradetail	None
Knee	1/4	74	PAR	Potter-Bucky diaphragm
Shoulder	1/4	74	PAR	Potter-Bucky diaphragm

* All exposed anteroposteriorly at 100 ma., 3 mm. Al filter and 40 inch distance, using 1 mm. focal spot.

milliampere-seconds were minimized by using a target-focal distance of 20 inches. Radiation scatter was controlled with a collimated beam. Intensifying screens were not employed except with the routine roentgenogram because of the loss of detail and the possible introduction of artefacts. Grids were excluded because they increased penumbra and any contrast enhancement gained by their use was offset by the increased kilovoltage requirement.

The no-screen and AA film were hand developed for 5 minutes at 68° F., while the M film was hand developed for 8 minutes. The routine screen film was developed in an automatic processor. A variable intensity illuminator was used for interpretation and extraneous light was controlled. The calculated skin and gonadal doses were within acceptable limits.

RESULTS

The roentgenograms were examined and ranked, based on our ability to detect the typical linear and punctate calcium pyrophosphate dihydrate deposits in the articular cartilage (Table III). Examples of the various joints examined are shown in Figures 1 through 4.

Table II

Joint	TECHNIQUE FOR AA AND M FILM (*Kodak Industrial*)* Time (sec.)	Kv. peak	TECHNIQUE FOR NO-SCREEN FILM (*Kodak Medical*)* Time (sec.)	Kv. peak
Hand and Wrist	2	39	2	31
Elbow	3	39	3	31
Ankle	3	42	3	35
Knee	4	46	4	40
Shoulder	4	46	4	40

* Films exposed at 200 ma., no added filter, no screen or grid and 20 inch distance using 1 mm. focal spot.

It was apparent that in most cases AA and no-screen film produced greater detail and contrast than screen films when the exposure factors given in Tables I and II were used (Fig. 5 and 6). In general, the roentgenograms made with type M film, exposed simultaneously with AA film, were underexposed, which accounts for their in-

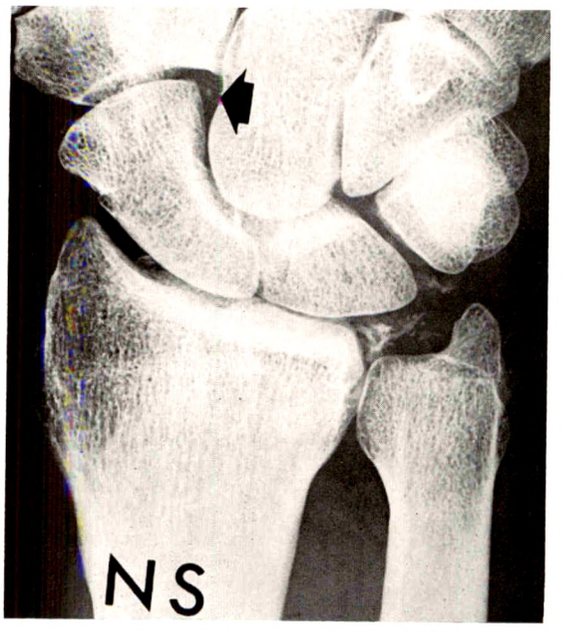


Fig. 1. Extensive chondrocalcinosis of pseudogout involving the ulnar-carpal disk and the articular cartilage of the carpal bones. The NS film (Kodak medical no-screen) demonstrates well a small deposit (arrow).

Table III

COMPARISON IN DETAIL AND CONTRAST OF THE 4 FILM TYPES EMPLOYED*

Joint		Routine Screen Film	Industrial AA Film	Industrial M Film	Medical No Screen
Hand and Wrist	right	0	11	3	11
	left	0	6	1	8
Elbow	right	0	7	1	8
	left	1	3	0	3
Knee	right	0	13	4	15
	left	0	10	2	11
Ankle	right	0	4	0	4
	left	0	5	0	6
Shoulder	right	0	7	4	5
	left	0	8	3	6

* The quality of each roentgenogram showing cartilaginous calcification was ranked by 2 observers and the best roentgenograms summarized for each joint. If no difference between 2 film types could be discerned, both were ranked as best.

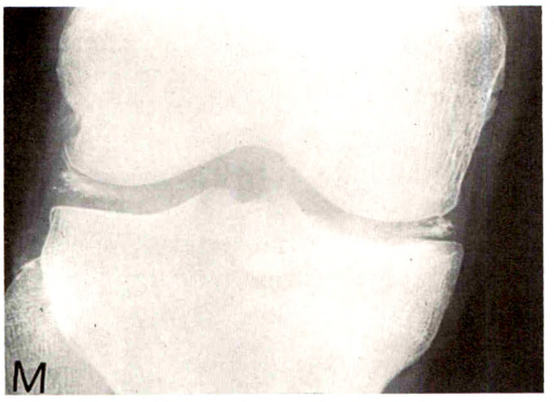


Fig. 2. Marked chondrocalcinosis of the menisci in the knee joint demonstrated on Kodak Industrial M film.

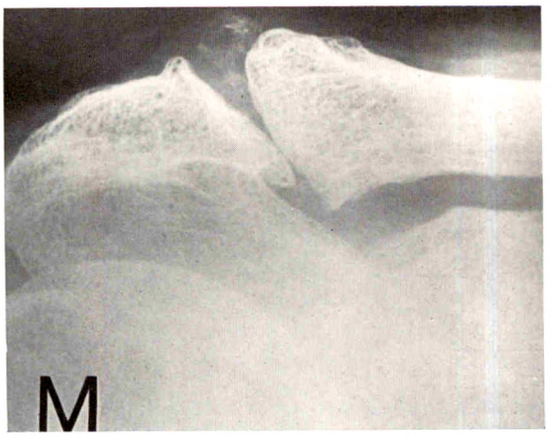


Fig. 3. Chondrocalcinosis of the acromio-clavicular joint demonstrated on Kodak Industrial M film.

feriority. We felt that the increase in milliampere seconds needed to bring the M roentgenograms to optimum density endangered the roentgenographic tubes, increased the patient dose and the possibility of patient motion and, therefore, was not desirable.

In only 1 of the 180 joints studied was the routine screen roentgenogram thought to demonstrate the intra-articular deposits as well as the industrial and no-screen roentgenograms. In no instance were calcifica-

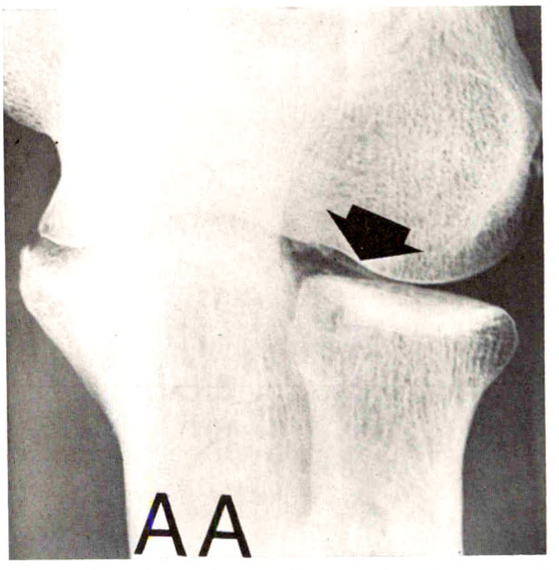


Fig. 4. Chondrocalcinosis of the elbow joint (arrow) demonstrated on Kodak Industrial AA film.

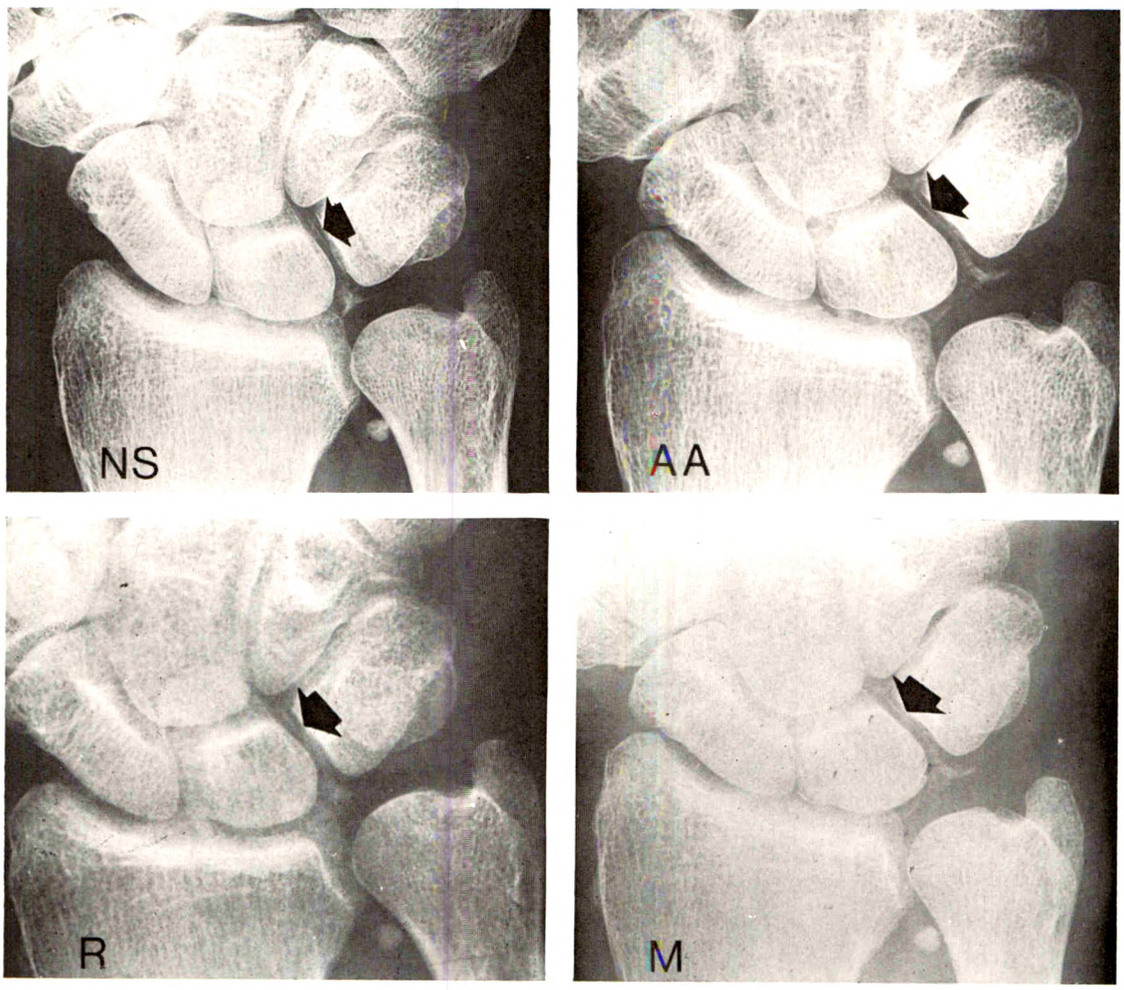


Fig. 5. Chondrocalcinosis of the wrist. Comparison of 4 types of film: Kodak medical no-screen (NS), industrial AA, industrial M and routine duPont Cronex II with screen (R).

tions detected on routine screen roentgenograms that could not be seen on the industrial or no-screen roentgenograms. In 20 joints the intra-articular deposits were not visualized at all on the routine screen roentgenograms but were readily observed on the industrial or no-screen roentgenograms (Fig. 7).

DISCUSSION

This study suggests that use of medical no-screen or industrial AA film, a small focal spot, a collimated beam with no added filtration and a 20 inch target focal distance will provide roentgenograms of maximum resolution and contrast. These qualities are highly desirable in the routine diagnosis of pseudogout, especially when the presence of calcified cartilage on routine roentgenograms is equivocal.

In population survey studies, an optimum technique would seem to constitute a *sine qua non*. While numerous roentgenographic diffraction studies of crystals recovered from joint fluid[9] and deposits obtained from numerous joints of 3 patients with pseudogout at necropsy[2] and from numerous joints of 7 anatomic cadavers[8] have all detected only calcium pyrophosphate dihydrate (CPPD), it is clear that the reverse is not true, *i.e.*, not all cartilaginous calcification is microcrystalline calcium pyrophosphate dihydrate. Solitary deposits of apatite and, in cadaver

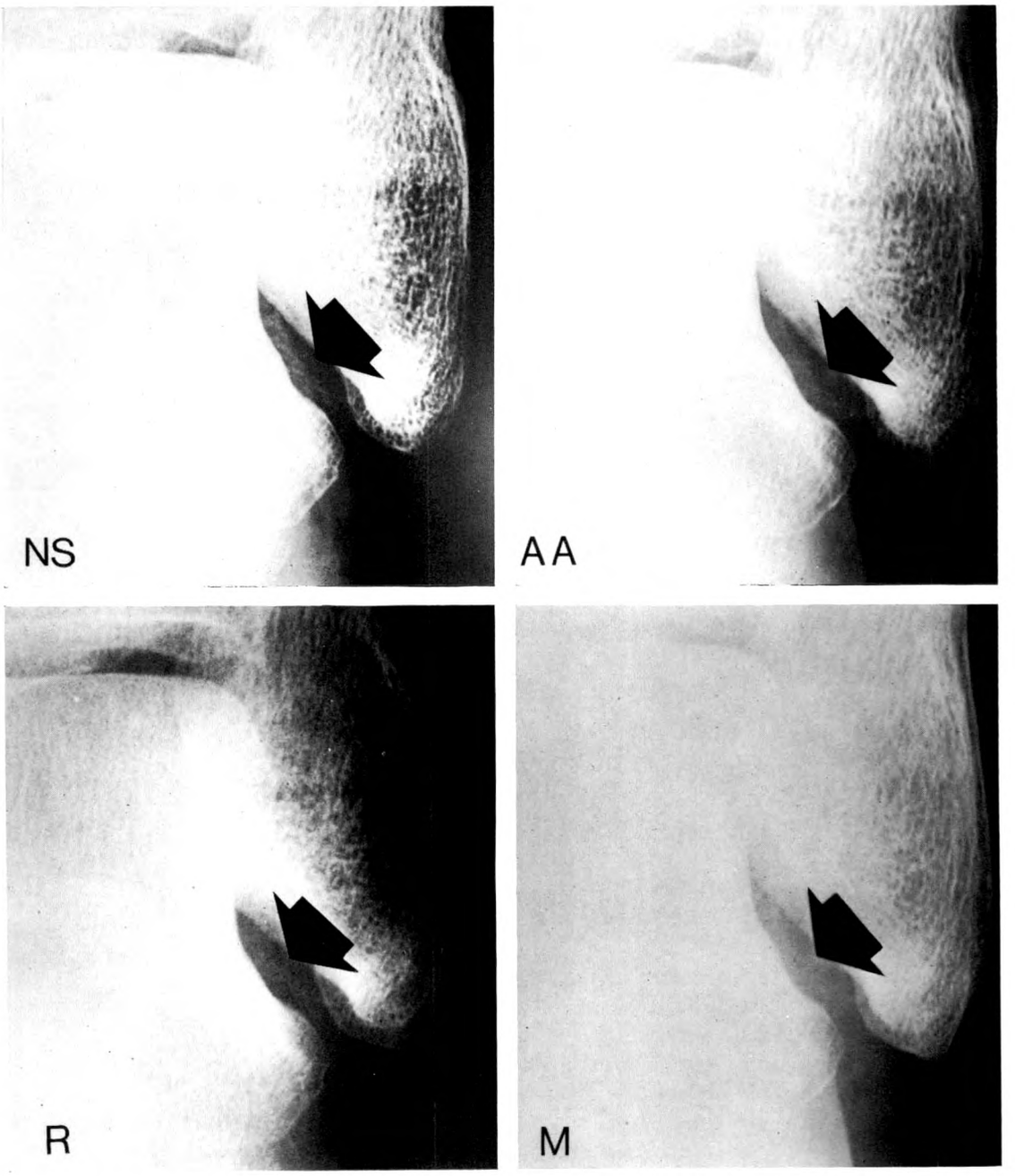


Fig. 6. Chondrocalcinosis of the ankle. Comparison of 4 types of film as in Figure 5.

cartilage at least, multiple punctate deposits of dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$) have also been identified.[8] *All chondrocalcinosis* is *not* associated with the pseudogout syndrome. Moreover, intra- and peri-articular vascular calcifications, which often show bilateral symmetry, may be confusing. Partially calcified osteophytes may also provide interpretative difficulty for the neophyte. The typical appearance of bilaterally symmetric punctate and linear calcifications in fibro and/or hyaline articular cartilage is *almost pathognomonic* for CPPD crystals.

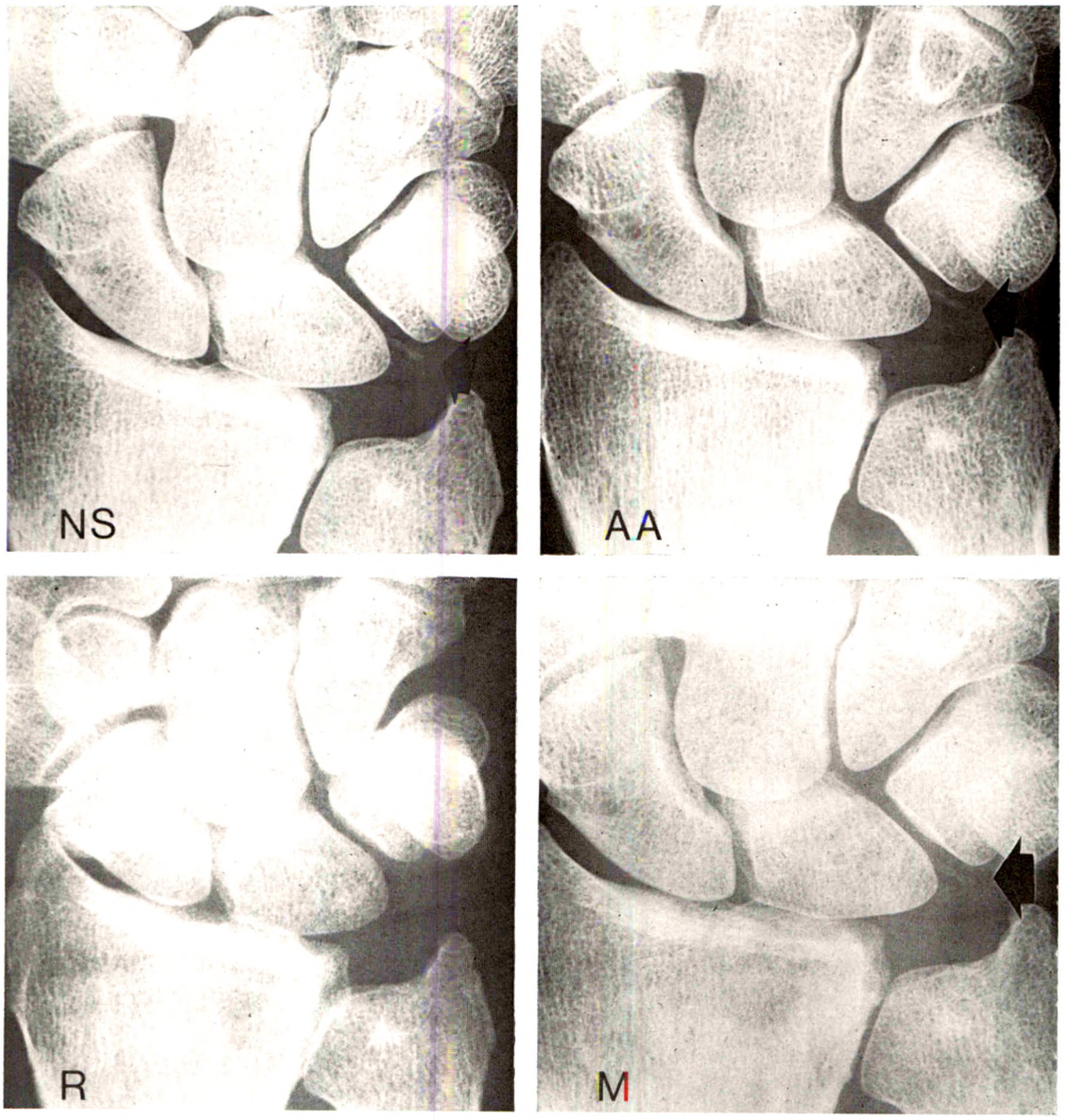


FIG. 7. Chondrocalcinosis of the wrist. Comparison of 4 types of film as in Figure 5. The articular calcification is not seen on the routine screen roentgenogram.

The identification of CPPD in multiple deposits in the menisci of 3.2 per cent of 215 anatomic cadavers[8] and the finding of calcifications of undetermined type in 7 per cent of an elderly population surveyed roentgenographically[1] suggest a prevalence sufficiently high to warrant inclusion of roentgenograms of the knees in population studies of arthritis.

There is little doubt that at least some cases of CPPD deposition disease are hereditary.[12] The techniques described in this paper may prove useful in family studies designed to further elucidate the genetic nature of this condition.

SUMMARY

Roentgenograms of 180 joints were made employing 4 different types of film in an attempt to define an optimum technique

for the study of pseudogout. Using the factors described, medical no-screen and industrial AA film were found to be best. Pseudogout (articular chondrocalcinosis) is defined by the presence of the calcium pyrophosphate dihydrate crystal. It is suggested that the technique described here provides a more reliable roentgenographic method for the detection of calcium pyrophosphate dihydrate crystal deposits in cartilage.

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COMPRESSION OF BLADDER DUE TO "RHEUMATOID" CYSTS OF HIP JOINT*

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RHEUMATOID arthritis is common but rarely do secondary manifestations of it directly affect the urinary bladder. In the case presented here, large, bilateral, soft-tissue, cystic masses developed in the pelvis of a patient with rheumatoid arthritis. Diagnosis was achieved only after laparotomy and biopsy. Because a review of available medical reports on rheumatoid arthritis failed to uncover a description of this manifestation, the following case is presented.

REPORT OF A CASE

A 43 year old white man was referred for evaluation of increasing urinary frequency, nocturia, dribbling, and mild dysuria during the preceding several months. He had no fever, chills, or hematuria.

He had had rheumatoid arthritis for 15 years, which had been treated with various drugs including steroids. Several reconstructive procedures had been performed on his hands and feet, which the arthritis affected primarily. Roentgenograms indicated extensive involvement of the left hip, but an apparently normal right hip.

Each occupied a lateral position and formed a bulging mass which projected medially. Intravenous pyelography and cystography confirmed their presence and indicated that they compressed the bladder from its inferior and lateral aspects (Fig. 1 and 2). The right mass appeared larger than the left. Neither contained calcification.

On digital rectal examination, two soft tissue masses could be felt in the pelvis. They were smooth and firm, the larger being on the right side. The masses were considered to be separate from the bladder and prostate. Cystoscopy disclosed compression of the lateral walls of the bladder almost to the midline.

Additional examinations included complete gastrointestinal roentgenography and left vasography (Fig. 3). The gastrointestinal and genital structures were apparently normal, but the bilateral pelvic masses were consistently demonstrated. Results of bone marrow study and laboratory examinations disclosed no abnormalities.

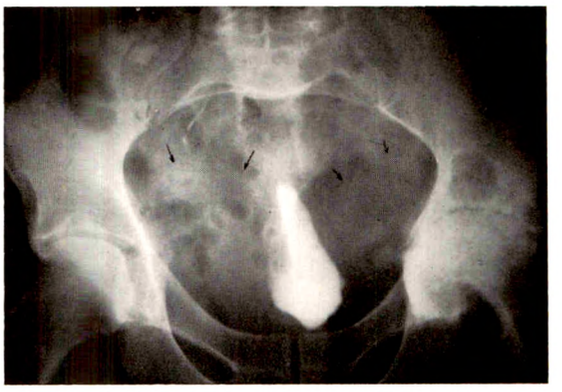


FIG. 1. Intravenous urogram shows small bladder compressed between the large soft tissue masses in both sides of the pelvis (arrows). Note severe rheumatoid arthritis of left hip with large cyst-like areas in bone above joint. Right hip appears normal.

The possibility of some relationship between the masses and the disease in the hip was con-

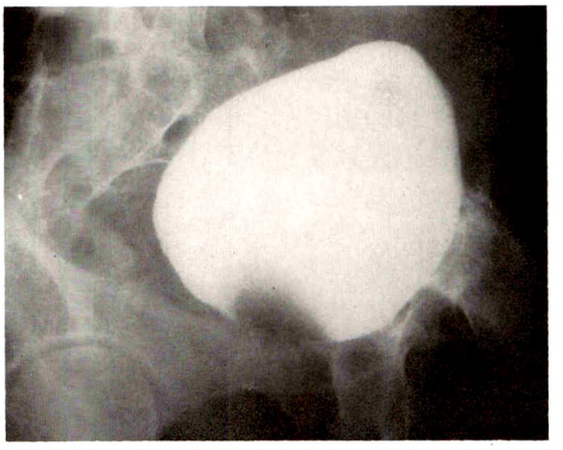


FIG. 2. Oblique cystogram shows indentation of distended bladder by the pelvic mass on one side.

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FIG. 3. Frontal roentgenogram after left vasography shows compression of bladder and upward and medial displacement of seminal vesicle on the left.

sidered but discounted as being unlikely. Because extensive examinations had not indicated the nature of the pelvic masses, exploratory laparotomy was advised. The preoperative diagnosis was "probably connective tissue tumors."

At exploration, the masses were not as large as one would have expected from the roentgenograms. This discrepancy may be explained on the basis of the increase in steroid medication. Two moderately large, smooth cysts were found along the respective contours of the pelvic wall in extraperitoneal position. The left cyst, which was unroofed and explored, contained only amber colored fluid. Examination of the base of the cyst revealed extension to the acetabulum.

Pathologic examination of tissue from the cyst wall and cell-block preparation of the fluid revealed chronic inflammatory changes, but no changes suggestive of malignant disease. No attempt was made to resect the cysts. The lesions were considered "rheumatoid cysts."

The patient recovered without incident and has continued to do well.

DISCUSSION

Rheumatoid arthritis and the "rheumatoid state" can involve most organs of the body in varying degrees, and may be manifest in diverse forms. Development of subcutaneous nodules and masses of granulomatous tissue adjacent to diseased joints is frequent.[2] Occurrence of subarticular synovial cysts is also well known,[3] and it is now recognized that involvement of hygromatous bursae is common.[4] The cystic masses in our patient are apparently comparable to bursal cysts and are different only because of their location, large size, and pressure effects. A recent editorial[1] described 14 bursae associated with the hip joint and stated that the involvement of one of the bursae may be the only manifestation of rheumatoid arthritis. Thus, development of "rheumatoid cysts or bursae" is certainly not unusual in this disease. It is interesting that the intrapelvic masses in our patient were essentially of equal size, despite the fact that one hip showed roentgenographic evidence of advanced rheumatoid arthritis, while the other appeared normal.

SUMMARY

Large, bilateral, pelvic, cystic masses were present in a 43 year old man with chronic rheumatoid arthritis. The cysts arose from the hip joints and compressed the bladder with resultant urinary symptoms. Biopsy indicated that their histologic appearance was compatible with that of "rheumatoid cysts," and the symptoms were controlled with steroid therapy. The location, size, and compressive effects of these cysts make this a unique case.

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PERSISTENT VOMERONASAL ORGAN*

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IN 1811 Jacobson[4] described a diverticulum in the nasal cavity of ruminants and rodents situated in the anteroventral part of the nasal septum, which he considered a glandular accessory olfactory organ. This structure and its nasal orifice had been described in man by Ruysch[11] in 1703, but he had attached no significance to it. Occasionally, some authors refer to the structure as the organ of Ruysch. Sommering also mentions this structure in his work on the organ of smell published in 1809. An extensive literature on the subject has accumulated with the most elaborate works by Broom[1] and v. Mihalkovics.[12]

In fishes, at one end of the animal spectrum, the organ is rudimentary, and in human adults it is retrogressive. In between these extremes, there are a variety of manifestations. The structure is not found in orders lower than fishes, and even in these—rather than a true organ, the structure is probably a homologue.

In most reptiles and in higher amphibia, the organ is highly developed and is present in addition to the true olfactory organ. In amphibians, Jacobson's organ appears first as paired areas of olfactory epithelium above the vomer bones which thicken and form anteroposterior gutters in the floor of the nasal cavity.

The grooves open into the oral cavity near the internal nares. In reptiles, the roof of the gutter closes in on each side, forming a tube lying below and internal to the nasal cavity and connected to the oral cavity by nasopalatine ducts which pass through the palate via the incisive foramina. Posteriorly, the tube ends blindly and is supplied by branches of the olfactory and trigeminal nerves. The olfactory nerve filaments may be divided into two distinct groups: (1) olfactory fibers terminating in the olfactory bulb, and (2) vomeronasal fibers terminating in the accessory olfactory bulb. In some reptiles, *e.g.*, snakes and lizards, Jacobson's organ appears to be a finer sense organ than the olfactory organ proper. It is completely separated from the other nasal structures and appears as two separate pouches on the roof of the mouth. Into these pouches, the tips of the bifid tongue are thrust after they have collected material from external objects being investigated.

In higher reptiles, such as crocodiles and chelonidans, as well as in birds, the organ is suppressed in the adult. In mammals it has been noted in a greater or lesser degree of development, with the higher development occurring in lower mammals.

Jacobson's organ is present in all orders of mammals; it is best developed in monotremes and marsupials; in primates it is rudimentary. It appears as a bilateral tubular structure lined with mucosa, blind posteriorly, situated in the anterior ventral part of the nasal septum, and opening in front in the region of the nasopalatine canal. Its communications vary. In most mammals, the duct opens into the nasopalatine duct with free communication with the oral cavity. In rodents and in man, the duct opens on the septal wall directly into the nose.

Hyaline cartilage surrounds the vomeronasal organ in mammals to a greater or lesser extent. In the cat, the cartilage capsule is complete anteriorly and incomplete posteriorly.[7] In the dog, it is incomplete in its entire extent. In those vertebrates in which the organ cannot be visualized, the cartilage accessory to the organ remains as an indication of its former presence. The vestigial cartilage remnant in man persists as the vomeronasal cartilage of the septum.

Most of the work on the anatomy and

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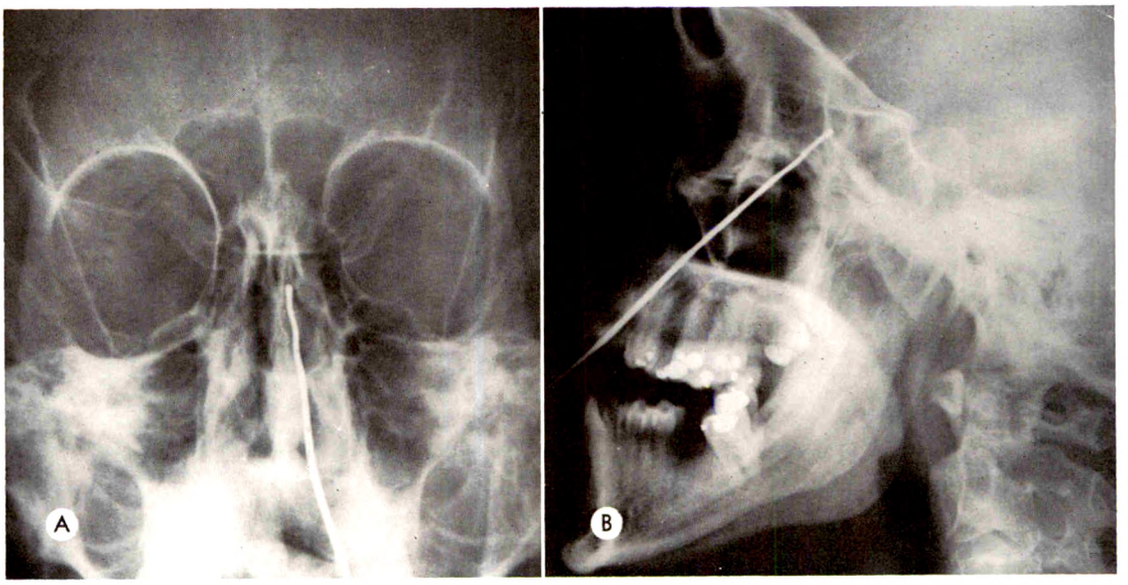


Fig. 1. Roentgenograms in the (*A*) anteroposterior and (*B*) lateral projection show the probe extending from the region of the alveolar socket of the medial incisor, through the nasopalatine cyst, and submucosally along the nasal septum.

comparative embryology of the vomeronasal organ was done during the 19th century; however, some attention has been paid to this structure in more recent years, mainly in the foreign literature.[2,3,8,13] Pearlman's[9] article is a classical review of the subject up to the year 1934. Because of the rarity of the clinically symptomatic and roentgenographically persistent vomeronasal organ, the case below is reported.

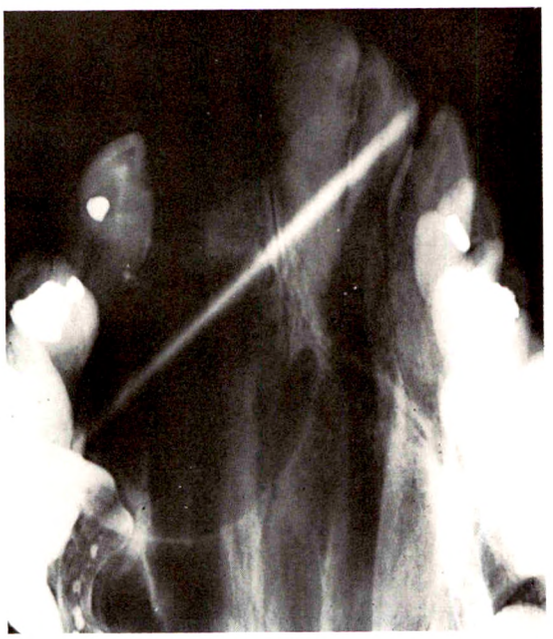


Fig. 2. An occlusal roentgenogram of the maxilla demonstrates the nasopalatine cyst in relation to the alveolar socket of the medial incisor. The linear density is an artifact.

REPORT OF A CASE

This 29 year old white male had a left upper central incisor extracted because of persistent pain. Since the extraction and several months prior to admission, there was intermittent discomfort and drainage from the involved alveolar socket. Roentgenograms of the alveolar margin demonstrated a cyst-like lesion resembling a cyst of the nasopalatine canal. By means of a polyethylene catheter inserted into the alveolar socket, the cyst was filled with opaque material, but showed no unusual extensions. A few days later the alveolar socket and cyst area were explored with a malleable probe, which passed easily without discomfort through the cyst area internally and cephalad submucosally along the nasal septum toward the sphenoid sinus (Fig. 1, *A* and *B*; and 2).

The patient underwent a submucous resection of the septum and curettage of the cyst area. He has had complete relief of symptoms for a period of 5 years.

DISCUSSION

Aberrations of development will frequently result in retention of structures of phylogenetic significance. The vomeronasal organ, an important olfactory organ in many vertebrates, is an atavistic remnant in man and probably of no functional significance. In adult man, its olfactory function is doubtful, but its function in general sensation is indicated by its innervation by the trigeminal and sympathetic nerves.

The vomeronasal organ is a constant structure in the human fetus and reaches its maximum development at approximately 20 weeks of gestation. Following this, degeneration may occur and it is not always present at birth. It is rarely found in the human adult in the opinion of most workers. Potiquet[10] in 1891 found the vomeronasal organ in 25 per cent of his patients. He noted that the narrowness of the orifice protects it from accidental penetration by probes, and that when the probe does enter no pain is felt.

Abnormal persistence of the vomeronasal organ has rarely been reported. Mangakis[6] described its presence in a young adult male who presented symmetrically on each side of the nasal septum fairly wide orifices opening in the nasal cavity. These were unusually long, measuring 6.2 cm. in length. Levin[5] reported a 25 year old male in whom the organ appeared as a mass and had been present since early youth. The mass diminished and reappeared, until at the age of 17 years it became progressively larger. More recently Fenu[2] reported 2 additional cases, 1 presenting bilaterally and the other unilaterally. These tubular cavities measured 1.5 cm. in length.

In the case here reported it is felt that the persistent vomeronasal organ communicated, as in many mammals, with the nasopalatine duct. Nonpatency of the oral aspect of the nasopalatine duct resulted in a cyst which in turn communicated with the persistent vomeronasal organ. Extraction of the incisor tooth apparently produced a communication between the alveolar socket and the cyst with resultant infection and drainage. With removal of the involved tissues, relief of symptoms was obtained.

SUMMARY

A case of a persistent vomeronasal organ is reported. Awareness of its presence resulted from its communication with a nasopalatine cyst which in turn communicated with an alveolar socket following tooth extraction.

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THE NORMAL HYPOGLOSSAL CANAL*

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SEVERAL cases of pathologic involvement of the bony hypoglossal canal have been observed in recent years at The University of Chicago. These cases are described in a separate article.[1,2] Since the review of the medical literature showed a surprising scarcity of any detailed anatomic description of this canal, the following study was performed to establish the normal roentgenographic anatomy of this forgotten canal.

ANATOMY

The hypoglossal canal runs outward and forward through the condyle of the occiput, transmitting the hypoglossal, or twelfth cranial nerve, a meningeal branch of the ascending pharyngeal artery and a plexus of emissary veins. The canal forms an angle with the sagittal, as well as with the orbito-meatal planes of the skull (Fig. 1; and 2, *A* and *B*). Both the right and left canal lie on or very near a line joining the external auditory canals. This relationship was found to be of help in determining the position of the canal for centering and for determining the level of the laminagraphic cuts.

The canal can usually be visualized in the oblique views of the skull which place the long axis of the canal perpendicular to the roentgenographic film, such as the Stenvers, the mastoid and the optic foramina views. However, the canal is then seen as a ring because it is looked at on end (Fig. 2*C*; and 3). Laminagraphy is essential in order to visualize the canal in the three dimensions and to examine its bony contours in detail.

TECHNIQUE

The canal was examined in three projections: (a) in its horizontal axis; (b) in its long axis; and (c) in cross section.



FIG. 1. Axial view of a dried skull specimen with the vertex removed. Metallic wires have been inserted in the mid-line (sagittal plane) and through the right hypoglossal canal. Metal rings were stuck in the outer and inner openings of the hypoglossal canals bilaterally.

(a) For the demonstration of the canal in its horizontal axis, the skull is placed in the axial or semi-axial position. The orbito-meatal line does not have to be exactly parallel to the table top, since the purpose of this view is the measurement of the angle formed by the hypoglossal canal with the sagittal plane of the skull. The central ray is directed to a point at the intersection of the midline and a line joining the right and left external auditory meati. The laminagraphic cuts are started at the level of the midpoint of the external auditory meatus and taken at 2 or 3 mm. intervals, moving toward the vertex. Usually, 6 ex-

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posures cover the area of the canals adequately (Fig. 2*A*).

(b) For the demonstration of the canal in its long axis, the skull is rotated from the lateral position with the side under investigation nearer to the table top until the sagittal plane makes an angle with the horizontal equal to the angle which the canal makes with the sagittal plane as measured in the axial projection. This will bring the long axis of the canal parallel to the table top. The orbito-meatal line should be perpendicular to the long axis of the table top so that the angle which the canal makes with the orbito-meatal line can be measured directly on the roentgenogram. The level at which the laminagraphic cuts are made will vary, depending upon the angle to which the skull is rotated. The central ray is directed to a point 2 inches anterior to the external auditory meatus. This view can also be called "zygomatico-mastoid" (Fig. 2*B*; and 4*A*).

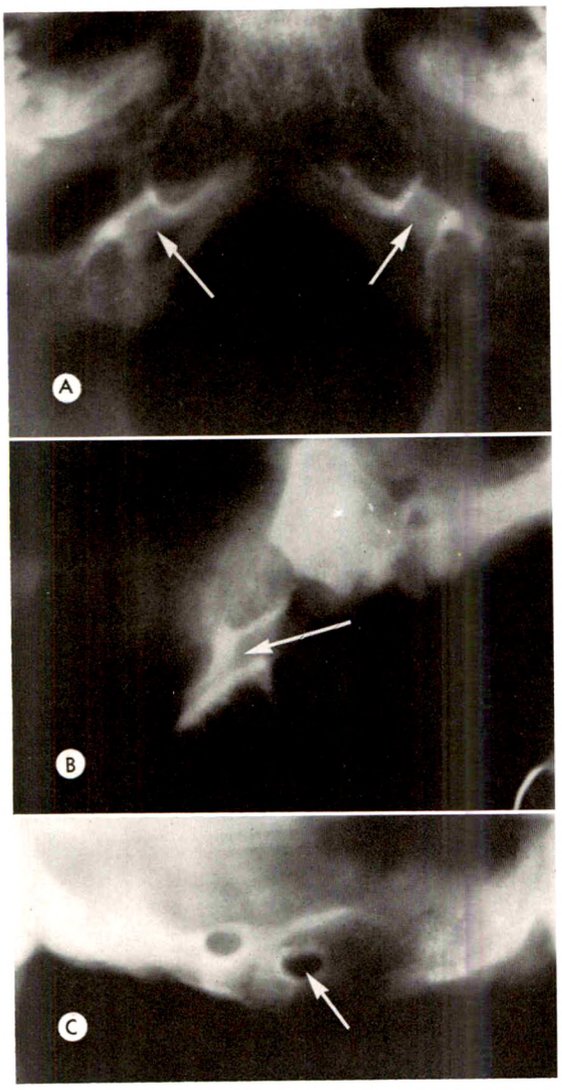


Fig. 2. The three projections in a dried skull specimen: (*A*) Axial laminagram at the level of the hypoglossal canals. (*B*) Laminagram in the zygomatico-mastoid projection showing the hypoglossal canal in its long axis. (*C*) Laminagram in the zygomatico-occipital projection showing the hypoglossal canal in cross section. Notice another foramen posterior to the hypoglossal canal—the condyloid canal.

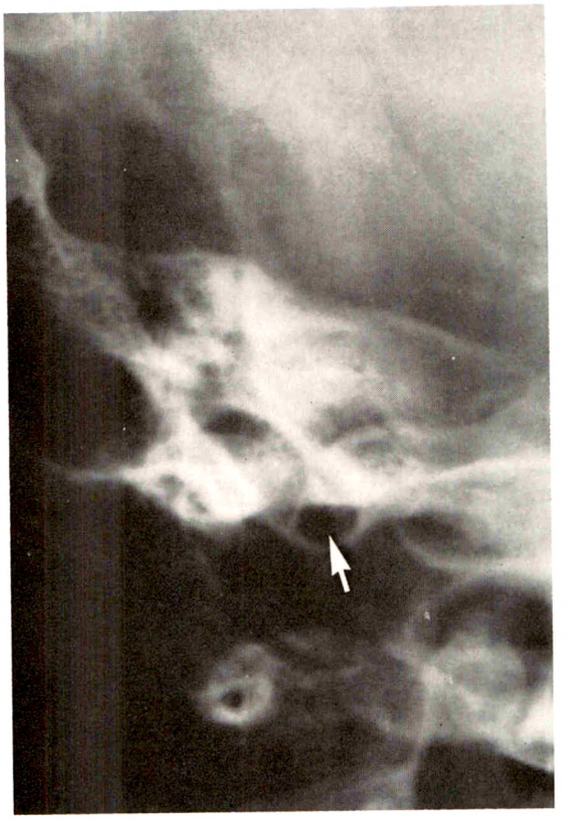


Fig. 3. Conventional Stenvers' view. The hypoglossal canal is seen on end.

(c) For the demonstration of the cross section of the canal, the skull is rotated from the face-up position away from the side to be examined until the sagittal plane makes an angle with the vertical equal to the angle which the canal makes with the sagittal plane as determined from the axial

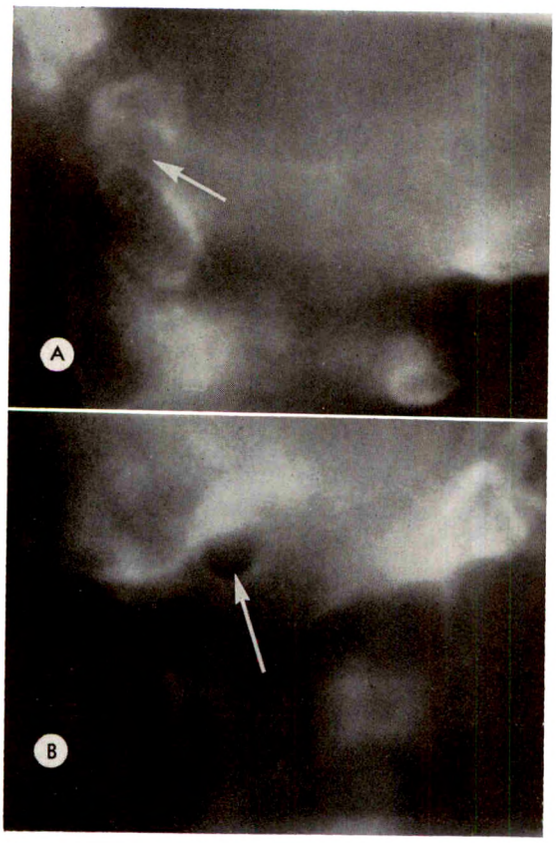


Fig. 4. Laminagrams in (*A*) zygomatico-mastoid and (*B*) zygomatico-occipital projections obtained in a patient.

projection. In order to correct for the angle which the canal makes with the orbito-meatal line, the skull should be tilted to the same degree and direction as determined from the zygomatico-mastoid view. The central ray is directed to the zygoma, about 1 inch in front of the external auditory meatus. This point varies, depending upon the angle to which the sagittal plane is rotated. The level of the laminagraphic cuts will also vary but is usually quite close to the posterior margin of the mastoid process. This projection may also be called "zygomatico-occipital" (Fig. 2*C*; and 4*B*).

RESULTS

Sixty-eight canals of 36 skulls were examined. Ten of these were from dried skull specimens. The remainder were patients having skull roentgenograms for various reasons unrelated to the hypoglossal nerve. Different parameters were measured. No correction was made for the known

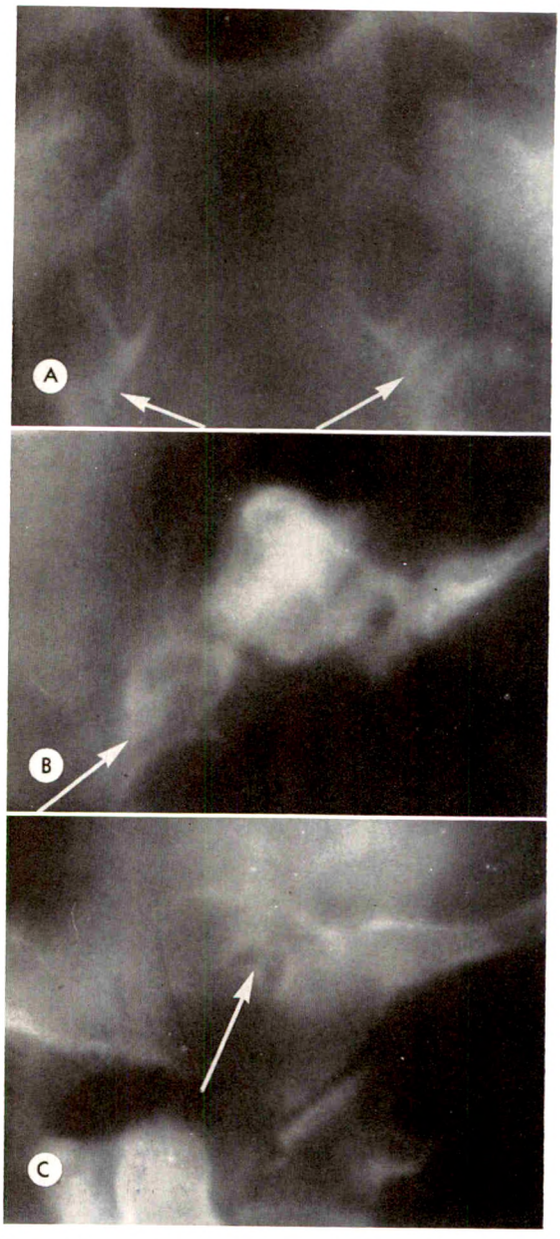


Fig. 5. Example of splitting of the hypoglossal canal at the inner opening. (*A*) Axial laminagram showing septa at the inner opening of both hypoglossal canals. (*B*) Laminagram in zygomatico-mastoid projection of the left hypoglossal canal showing a septum hanging down from the roof of the canal near the inner opening. (*C*) Laminagram in zygomatico-occipital projection at the inner opening of the canal, which appears to be divided in three compartments.

constant magnification of 30 per cent inherent to the apparatus used for this study.

INCLINATION

A. The angle with the sagittal plane. This is determined in the axial projection. The maximum angle was 55° and the minimum 20°. The average was 37°. A variation up to 25° was found between the angles of the right and left canals of the same subject.

B. The angle with the plane of the base of the skull. This is determined from the zygomatico-mastoid projection. The maximum angle was 22° upward and forward; the minimum 5° downward and forward. The average angle was 7° upward. In only 21 skulls could this angle be compared on the two sides. A variation up to 10° was found.

CURVATURE

Forty-nine canals (72 per cent) showed some degree of upward convexity when viewed lengthwise (Fig. 4*A*). The rest were straight (Fig. 2*B*).

Both sides were consistent in this appearance except in 2 instances, when one side was straight and the other arched upward.

OUTER OPENING

This opening faced forward and laterally. On the average, it was oval, measuring 7×6 mm., with the long axis horizontal. The longest diameter was 11 mm. and the shortest 4 mm.

INNER OPENING

This faced posteriorly and medially. On the average, it was oval, with the long axis horizontal. The average measurement was 7.5×6 mm. The long axis was slightly larger than that of the outer opening because the average figure was affected by several cases where the canal was split by a bony septum; this septum was almost in all cases on the inner opening. The smallest diameter was 4 mm. and the largest 12 mm.

Comparison was made between the outer and inner openings of the same canal. A difference up to 4 mm. was found between the two openings. The highest figures were obtained in axial projection of the skull.

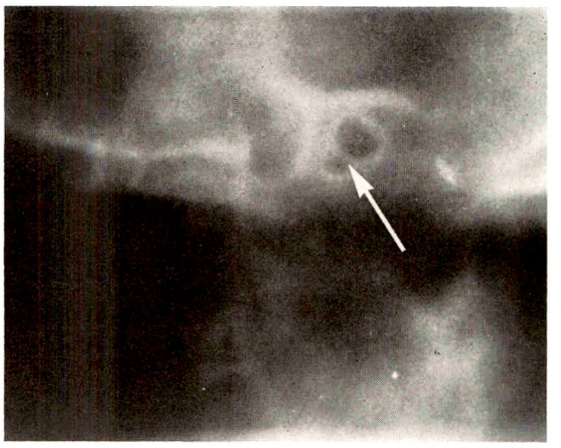


Fig. 6. Laminagram in zygomatico-occipital projection showing splitting of the hypoglossal canal at the outer opening.

THE MID-CANAL

This tended to be rounded, with an average of 6 mm. in diameter. The smallest diameter was 4 mm. and the largest 11 mm.

When the two sides of the same skull were compared, a variation up to 3 mm. was found. The greatest difference was seen in the zygomatico-occipital projection.

LENGTH

As determined on the zygomatico-mastoid projections, the average length was 11 mm.

The difference in length between the two canals of the same subject did not exceed 5 mm.

SPLITTING

Thirteen of the canals were septate. In 4 skulls, the septa were bilateral (Fig. 5, *A*, *B* and *C*). Except for 1 case (Fig. 6), the septum was at the inner opening.

CONTOUR

The contour of the canal usually was smooth with the cortex intact. However, some canals had cystic areas adjacent to them, connected to their lumen. These

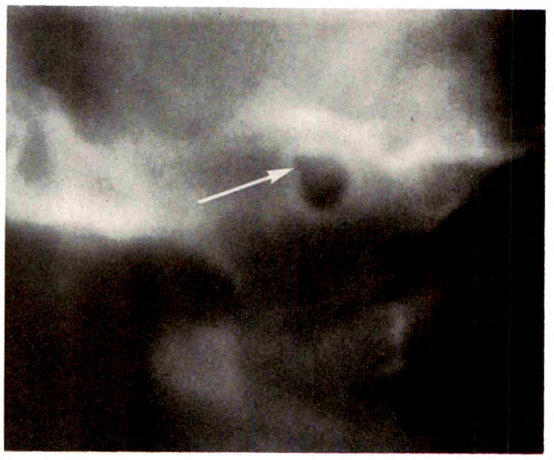


FIG. 7. Laminagram in zygomatico-occipital projection showing a small corticated outpouching of the anterior wall of the canal near the roof.

cystic areas are usually well defined and may even be corticated (Fig. 7).

SUMMARY

1. From the previous experience with laminagraphy of the skull base, it became evident that pathology of the hypoglossal canal is not as rare as the medical literature would indicate.

2. A technique is described for the roentgenographic examination of the canal.

3. Detailed anatomy of the normal canal and its normal variations are described.

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THE ABNORMAL HYPOGLOSSAL CANAL*

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THE use of body section roentgenography for the study of the base of the skull has allowed us to find a surprisingly large number of cases with pathologic involvement of the hypoglossal canal. This appears even more surprising if one considers the great scarcity in the radiologic literature of reports concerning the pathology of the canal for the twelfth cranial nerve. This scarcity results from the difficulty of visualizing the hypoglossal canal in conventional roentgenograms.

Shapiro and Janzen[11] mention that in the Towne view the hypoglossal canal appears as a foramen about 4×5 mm. in diameter, superior to the foramen magnum. Some frontal body section roentgenograms of the dried skull are included in his book, to demonstrate the canals on both sides. The canal may be seen in Stenvers' and other views where the skull is roentgenographed in an oblique position. However, the hypoglossal canal is not always demonstrated in these views and, when visible, the superimposition of other bone structures may prevent a proper evaluation of the canal.

In searching the literature, the only relevant articles found were those of case reports of hypoglossal nerve neurinomas. These tumors can be either extracranial or intracranial. Apparently, so far, there have been only 9 cases of intracranial tumors described in the world literature. We have been able to find only 3 reports mentioning preoperative roentgenologic findings. No mention is made whether body section roentgenography was used in any of these cases.

ANATOMY

The canal on either side pierces the base of the occipital condyle above the level of the foramen magnum. It transmits the hypoglossal or twelfth cranial nerve, a meningeal branch of the ascending pharyngeal artery and a network of emissary veins. In Gray's Anatomy[2] the canal is described as directed lateralward and forward. It may be divided by a bone spicule.

MATERIAL

We have found 14 cases in which the hypoglossal canal appeared roentgenologically abnormal. Thirteen of these cases have been definitely proved. One of the cases has not yet been confirmed by surgery. In the 13 proven cases, three types of involvement have been found:

(1) The canal may be involved by lesions occurring in the twelfth cranial nerve (single neurinomas and generalized neurofibromatosis). Two cases of this type were found.

(2) The canal may be involved by direct extension of an adjacent neoplasm or by hematogenous metastases (glomus jugulare tumors, chordomas, primary cholesteatomas, meningiomas and various primary malignant tumors). Of this type, 8 cases are included.

(3) The bony boundaries of the canal may be involved in a primary disease of the bone, such as Paget's disease, osteomyelitis and fibrous dysplasia. Three cases of this type are included.

The involvement of the canal is not necessarily associated with neurologic symptomatology and certainly the two features may not occur simultaneously. The neurologic symptoms usually precede the roentgenographic findings in cases of twelfth nerve tumors, but often follow them in other types of involvement. In 2 of our cases (Cases 5 and 8), there was complete lack of neurologic findings at the time we noted the involvement of the hypoglossal canal. A few months after the roentgenographic demonstration, clinical

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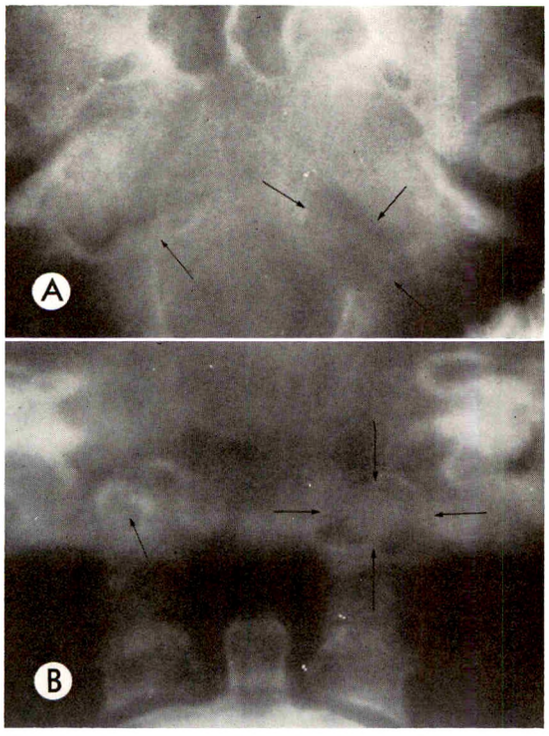


FIG. 1. *Neuroma.* Case 1. (*A*) Axial laminagram showing a 3.0 cm. area of destruction about the left hypoglossal canal extending from the foramen magnum to the jugular fossa. (*B*) Frontal laminagram showing ballooning of the left hypoglossal canal.

evidence of twelfth nerve palsy became manifest.

REPORT OF CASES

CASE 1. This 51 year old female was first seen complaining of nausea and vomiting, loss of appetite and weight, and headaches radiating from the back of the neck to the front, more sharp on the left side. Physical examination showed deviation of the tongue to the left with tremors and marked atrophy of the left side of the tongue. There were also signs of involvement of the 5th, 7th and 8th cranial nerves. The cerebrospinal fluid proteins were 116 mg. per cent. A conventional skull roentgenogram showed no abnormality. Laminagrams, however, showed a large area of destruction in the region of the left hypoglossal canal encroaching on the jugular foramen (Fig. 1, *A* and *B*). A suboccipital craniotomy was performed and a tumor was found extending through the hypoglossal canal, compressing the left side of the medulla. The tumor was successfully removed. At the histopathologic examination, the specimen appeared to be a typical neuroma arising from the hypoglossal nerve.

CASE 2. This 55 year old female with generalized neurofibromatosis complained of episodic pain originating in the left preauricular area and radiating to the left supraorbital ridge. She had some difficulty in moving the tongue but denied any dysarthria. On physical examination there were signs of involvement of the 9th, 10th and 11th cranial nerves and hemiatrophy of the left side of the tongue, which deviated to the left. She also had left hemiparesis. Conventional skull roentgenograms showed some enlargement of the left jugular fossa. Laminagrams revealed ballooning of the left hypoglossal canal and of the left jugular foramen, with erosion of the inferior aspect of the petrous pyramid. There was also some widening of the right hypoglossal canal (Fig. 2, *A* and *B*). A pneumoencephalogram showed nonvisualization of the left cerebellopontine

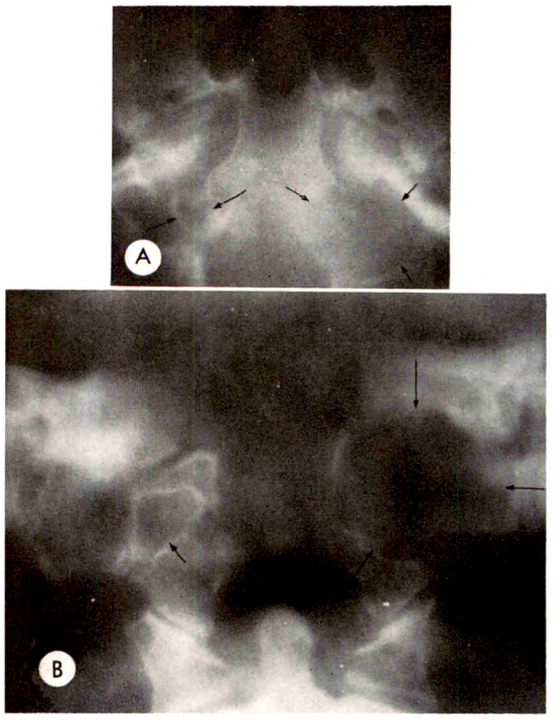


FIG. 2. *Neurofibroma.* Case 2. (*A*) Axial laminagram of the skull with unequivocal enlargement of the left and strong suggestion of enlargement of the right hypoglossal canal. (*B*) Frontal laminagram showing the marked expansion of the left hypoglossal canal. Again, the right hypoglossal canal appears moderately enlarged.

angle cistern. A suboccipital craniotomy was performed and a neurofibroma of the left hypoglossal nerve was excised.

Case 3. This 20 year old female with generalized neurofibromatosis had surgery at another hospital with a report of regular, fusiform and cylindrical enlargements of the left 9th, 10th, 11th and 12th cranial nerves and of the cervical portion of the sympathetic system, including the middle and superior ganglia. Histologic studies of the biopsies from these tumors led to the diagnosis of a meningioma. Follow-up showed progression of the extension into the base of the skull and left vocal cord paralysis. On physical examination at the time of admission to this hospital, the olfactory function was diminished on the left and there were signs of involvement of the sensory portion of the 7th cranial nerve and of some loss of motor function of the tongue. Roentgenologic studies showed asymmetry of the base of the skull due to hyperostosis on the left. The changes in the skull were better visualized on laminagrams, which also showed encroachment upon the left hypoglossal canal.

Case 4. This 70 year old female had headaches and hearing loss for the past year. On physical examination, there were signs of involvement of the 5th, 8th, 9th and 10th cranial nerves, but the 12th was not involved. Conventional roentgenograms demonstrated destruction of the right petrous apex, petrous ridge and mastoid, as well as some involvement of the clivus. At laminagraphy, a large destructive lesion of the floor of the middle and posterior cranial fossae was confirmed. The hypoglossal canal was included in the destruction (Fig. 3). The cerebrospinal fluid proteins were 44 mg. per cent. At exploratory craniotomy, a large tumor mass was found in the right side of the posterior cranial fossa, which at biopsy proved to be a meningioma.



Fig. 3. *Meningioma.* Case 4. Frontal laminagram showing destruction of the right petrous bone and right occipital condyle, including the hypoglossal canal.



Fig. 4. *Primary cholesteatoma.* Case 5. Frontal laminagram showing amputation of the right petrous apex and destruction of the right occipital condyle, including the hypoglossal canal. The left side is normal.

Case 5. This 57 year old male complained of progressive tinnitus and bilateral hearing loss of 4 years' duration and intermittent right suboccipital pain. On physical examination, there was weakenss of the right upper face. A large destructive lesion of the base of the skull was demonstrated by conventional studies. Laminagraphy showed the exact extent of the tumor and revealed involvement of the right hypoglossal canal (Fig. 4). A few months later a right 12th nerve palsy became manifest. At surgery, a primary cholesteatoma was removed from the posterior cranial fossa. It extended from the right mastoid process along the floor of the skull, eroding the petrous pyramid, the basiocciput and basisphenoid and reached the brain stem. The tumor embraced the 7th and 8th cranial nerves.

Case 6. This 42 year old male was first seen in another hospital with difficulty in blowing his nose, labored breathing and dysarthria. A smooth, rounded mass was noted in the left nasopharynx. Conventional roentgen examination revealed a large soft tissue mass in the nasopharynx with destruction of the base of the skull in the region of the sphenoid sinus and middle cranial fossa on the left. Laminagraphy

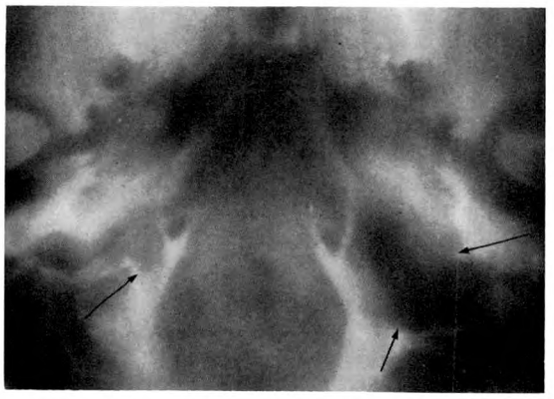


FIG. 5. *Glomus jugulare tumor.* Case 8. Axial laminagram showing enlargement of the left jugular fossa with destruction of the posterolateral wall of the hypoglossal canal.

showed erosion and destruction of the clivus, mostly on the right and inferiorly, with extension into the petro-occipital fissure. The right hypoglossal canal was certainly involved. Laminagraphy also showed an area of destruction in the right lateral mass of the atlas, which was not suspected from conventional study. At surgery, a large tumor was found in the nasopharynx, 90 per cent of which was removed. It proved to be a chordoma. He was given radiotherapy. Three years later he had recurrence of a mass, diplopia, bilateral 6th nerve palsy and signs of 12th nerve palsy on the right, with atrophy of the tongue muscle but no fibrillations.

CASE 7. This 57 year old female complained of a roaring noise in the right ear corresponding to the pulse beat of 1 year's duration, as well as right temporo-occipital headaches for several years. A glomus tumor was removed from the middle ear. Five years later, hearing was completely lost. Twelve years after the operation, she noticed weakness of the right side of the face, which was progressive. A year later she developed ectropion, lagophthalmos, tongue weakness with loss of taste and difficulty in swallowing. On physical examination, she had signs of involvement of the 5th, 7th, 9th, 10th and 12th cranial nerves. A large destructive process involving the apex of the right petrous pyramid was demonstrated on conventional roentgenograms as far back as 1947. Laminagraphy showed a large destructive process in the region of the right jugular fossa with almost complete destruction of the right petrous pyramid and encroachment on the occipital condyle with involvement of the right hypoglossal canal.

CASE 8. This 23 year old female, $1\frac{1}{2}$ years prior to admission, noted diminished acuity in the left ear with noises; there were short periods of vertigo. At neurologic examination, the cranial nerves were intact. The diagnosis was glomus jugulare tumor by biopsy. Conventional roentgenograms showed enlargement of the left jugular fossa. Laminagraphy confirmed the destructive process of the osseous structures surrounding the left jugular fossa, including the hypoglossal canal except for its anteromedial wall (Fig. 5). A few months later, weakness and deviation to the left of the tongue became manifest.

CASE 9. This 53 year old male complained of headaches localized to the vertex of 8 months' duration, loss of weight and plugged ears. Cervical lymphadenopathy was present. A mass was seen in the nasopharynx which, at biopsy, was a poorly differentiated squamous cell carcinoma. There were no abnormal signs in the tongue. Conventional roentgenograms showed a soft tissue mass in the nasopharynx. Laminagraphy demonstrated destruction of the clivus and left occipital condyle with involvement of the hypoglossal canal.

CASE 10. This 56 year old female, with carcinoma of the breast, was admitted with a chief complaint of difficulty in swallowing. On examination, the tongue was weak on the right side. Two months later, following endocrine therapy, the signs of right hypoglossal nerve palsy completely disappeared. Bilateral adrenalectomy and oophorectomy were performed. Subsequently, she developed 6th nerve paralysis, difficulty in swallowing and talking, diminished hearing in the right ear and occipital pain. On physical examination, there was atrophy and weakness of the right side of the tongue with deviation. Conventional skull roentgenograms revealed no destructive lesions in the base of the skull. Laminagraphy, however, demonstrated a destructive lesion extending from the right jugular fossa to the right anterior foramen lacerum with involvement of the adjacent aspects of the left petrous pyramid and occipital bone, including the hypoglossal canal (Fig. 6).

Case 11. This 47 year old male diabetic had a left mastoidectomy for mastoiditis 2 months prior to admission. Following surgery, the patient developed occipital headache, vertigo and double vision. On physical examination, the tongue deviated to the left and its left side was atrophied; there was also left 6th nerve paresis. The cerebrospinal fluid proteins were 108 mg. per cent and there were 80 cells per cc., of which 12 were white blood cells. Conventional roentgenograms showed a destructive lesion of the medial portion of the undersurface of the left petrous pyramid and jugular foramen. Laminagraphy showed that this lesion involved the adjacent portion of the left petrous and occipital bones, including the left hypoglossal canal. At left posterior fossa exploration, no intradural lesion was found, but the apex of the left petrous pyramid and the floor of the posterior cranial fossa were seen to be soft and involved in an inflammatory process. Biopsy showed only inflammatory changes.

Case 12. This 71 year old female had Paget's disease of the skull. Serum alkaline phosphatase was 46.8 King-Armstrong units. She developed hearing loss in both ears and screeching noise. On examination, there was bilateral nerve type deafness but no signs of tongue motor involvement. Cerebrospinal fluid proteins were 54 mg. per cent. There was roentgenologic evidence of Paget's disease of the skull. Laminagrams showed a "washed out" appearance of the involved bones.

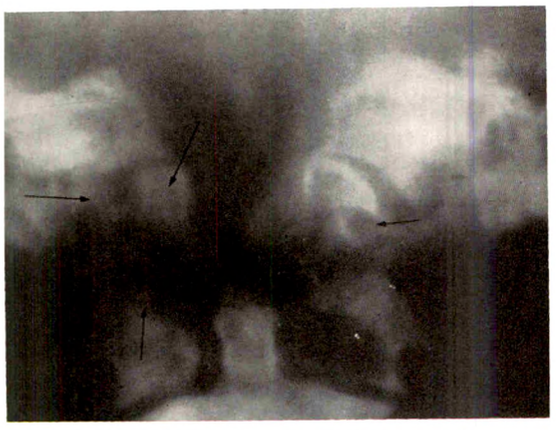


Fig. 6. *Metastatic carcinoma of the breast.* Case 10. Frontal laminagram showing destruction of the right occipital condyle, including the hypoglossal canal, and of the adjacent part of the petrous pyramid. Note also, the destruction of the lateral masses of the atlas, especially on the left side.

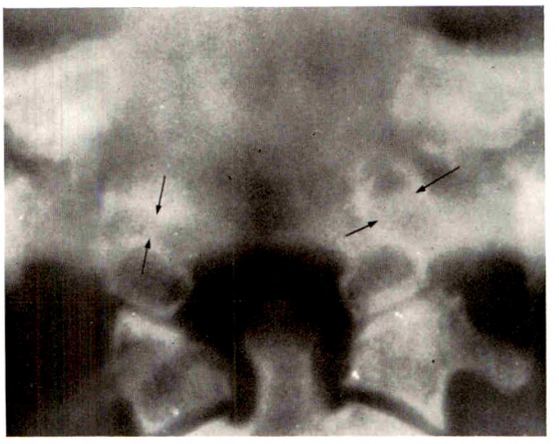


Fig. 7. *Neurinoma.* Case 14. Frontal laminagram showing an obvious discrepancy in size between the hypoglossal canals. The left one measures 12 mm. in diameter, the right one is only 4 mm. in diameter. This case has not yet been confirmed by surgery.

Case 13. This 60 year old female was a known case of Paget's disease of the skull who developed 8th nerve paralysis on the left. There was no clinical evidence of other cranial nerve affections. Roentgenograms showed advanced Paget's disease of the skull. Laminagraphy showed a "washed-out" appearance of the bones; the hypoglossal canals were ill-defined on both sides.

Case 14. This was a 41 year old male whose chief complaint was hissing of the left ear with diminished hearing for 10 years. One month before admission, he was awakened by a roaring sound in the ear. Cerebrospinal fluid proteins were 29 mg. per cent. Neurologic examination and pneumoencephalography were negative. Conventional skull roentgenograms were negative. Laminagraphy showed enlargement of the left hypoglossal canal consistent with a neurinoma of the 12th cranial nerve (Fig. 7). No surgery was performed.

DISCUSSION

Table 1 summarizes the data concerning the 13 proven cases of pathologic involvement of the hypoglossal canal. From this, it is evident that the spectrum of pathology is

TABLE I

Case No.	Age	Sex	Diagnosis	Clinical Evidence of 12th Nerve Palsy at Time of Roentgen Studies	Conventional Roentgenographic Skull Changes	Conventional Roentgenographic Hypoglossal Changes	Laminagraphic Hypoglossal Changes
1	51	F	Neurinoma	+	Nil	Absent	Present
2	55	F	General neurofibromatosis	+	Jugular fossa enlargement	Absent	Present
3	20	F	Von Recklinghausen's neurofibromatosis with meningioma	+	Skull asymmetry and hyperostosis	Absent	Present
4	70	F	Meningioma	−	Skull base destruction	Absent	Present
5	57	M	Primary cholesteatoma	−	Skull base destruction	Absent	Present
6	42	M	Chordoma	+	Soft tissue mass of nasopharynx	Absent	Present
7	57	F	Glomus jugulare tumor	+	Petrous apex destruction	Absent	Present
8	23	F	Glomus jugulare tumor	−	Jugular fossa enlargement	Absent	Present
9	53	M	Invading nasopharyngeal carcinoma	−	Soft tissue mass of nasopharynx	Absent	Present
10	56	F	Metastasizing carcinoma of breast	+	Nil	Absent	Present
11	47	M	Osteomyelitis of skull base	+	Skull base destruction	Absent	Present
12	71	F	Paget's disease	−	Paget's changes	Absent	Present
13	60	F	Paget's disease	−	Paget's changes	Absent	Present
14	41	M	Not confirmed	−	Nil	Absent	Suspected

broad. There are, however, some characteristic roentgenologic features for each type of lesion which should help in the differential diagnosis. These can be summarized as follows.

Neurinomas and neurofibromas. These produce expansion of the hypoglossal canal toward both the foramen magnum and the jugular fossa (Cases 1 and 2).

Meningioma. These can involve the hypoglossal canal either by hyperostosis of the surrounding bone structures (Case 3), or by bone destruction (Case 4).

Primary cholesteatoma and chordoma. These produce destruction similar to that produced by the destructive type of meningioma (Cases 5 and 6). However, in chordoma the concomitant involvement of the clivus and upper cervical spine provides a valuable clue to the diagnosis.

Glomus jugulare tumor. The destruction of the hypoglossal canal from the anterolateral or jugular aspect is a useful feature, especially when associated with erosion of the inferior aspect of the petrous pyramid (Cases 7 and 8).

Malignant tumors involving the hypoglossal canal, either by direct extension or hematogenous spread, produce ill-defined destruction of the osseous structure due to infiltration of the bone (Cases 9 and 10).

Active osteomyelitis produces changes in the bones which are indistinguishable from those produced by neoplastic infiltration.

Paget's disease gives on laminagrams a characteristic "washed-out" appearance of the bones so that the structures become completely unrecognizable. The absence of 12th cranial nerve symptomatology in our cases is presumably due to the fact that there was no encroachment upon the lumen of the canal, as might occur in this disease (Cases 12 and 13).

The fact that at The University of

Chicago we were able to collect this series over a period of 3 years proves the following two facts:

(1) Pathology of the hypoglossal canal is much more frequent than one is led to believe by reviewing the literature. One should consider, for instance, that we came across 2 proven cases of hypoglossal nerve tumors and a strongly suspected third case, whereas there are only 9 cases described in the world literature since 1934. Raney *et al.*[9] mentioned that the apparent rarity of such cases is probably related to the fact that symptoms usually develop late and are so precipitous that many of these patients die suddenly before the diagnosis can be made.

(2) Laminagraphy is essential for the roentgenologic demonstration of the canal. At The University of Chicago, laminagrams of the skull over the last 3 years have been made at a much higher rate than they were previously.

All the cases described were examined by the three orthogonal views: axial, frontal and lateral, as routinely done for the study of the base of the skull, particularly by laminagraphy Whereas the axial projection is often satisfactory as it runs along the long axis of the hypoglossal canal, the frontal and lateral projections give an oblique section of the canal. In order to obtain a true image, the head should be obliqued to correct for the inclination of the canal.

During our work, it became clear to us that the hypoglossal canal is variable in size and shape. A knowledge of the anatomy of the normal canal and its variation is, therefore, important. The occurrence of equivocal cases (the right hypoglossal canal in Case 2 [Fig. 2, *A* and *B*] and Case 14 [Fig. 7]) is the result of this lack of knowledge.

SUMMARY AND CONCLUSION

1. Thirteen proven cases of involvement of the hypoglossal canal are presented.

2. Abnormalities of the hypoglossal canal seem to be more common than is suggested by the world literature.

3. The occurrence of subtle changes, both normal and abnormal, plus the oblique direction of the canal initiated a study at The University of Chicago to devise a roentgenographic technique for the examination of the canal and to establish the normal appearance and dimensions of the hypoglossal canal.

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CRANIOMETAPHYSEAL DYSPLASIA (PYLE'S DISEASE) IN AN ANCIENT SKELETON FROM THE MOCHICA CULTURE OF PERU*

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THE most highly developed civilizations which preceded the Inca Empire in Perú were those of the desert kingdoms of the Mochicas and Chimús. The Mochica culture developed between the years 200 A.D. and 800 A.D. and was succeeded by that of the Chimús who in 1461 were overwhelmed by the Incas. The Mochica-Chimú civilizations developed in the coastal deserts of northern Perú and the dry desiccating sands of these areas have preserved large quantities of their skeletal remains in a remarkably good state for paleopathologic study. Their dead were buried along with their possessions so that an approximate archeologic appraisal of the time in which they lived can be obtained. Radiocarbon studies, of course, provide a more accurate means of dating.

Among the many osseous remains recovered from ancient cemeteries in the Chicama valley of northern Perú is the lower half of an unusual skeleton, the tubular bones of which have a pronounced splaying at their ends (Fig. 1). The Chicama valley is considered to be the heartland of the Mochica culture and the ceramics, textiles and utensils found in the cemetery from which these bones were recovered are archeologically identified as those of the Mochica culture. The upper part of the skeleton, with the exception of one humerus, had been destroyed by grave diggers.

The excellent state of preservation of the bones made roentgenographic and gross pathologic examination most rewarding. On roentgen examination, the upper portion of the humerus showed marked splaying

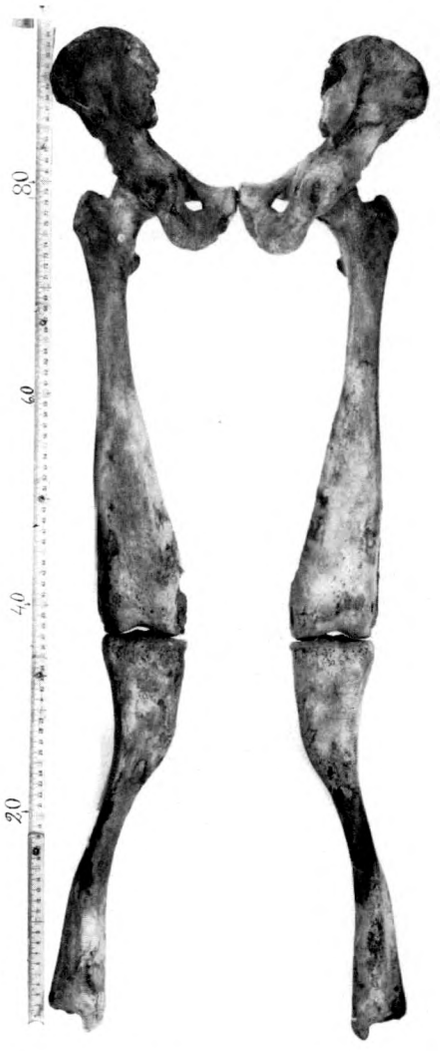


FIG. 1. Pelvis and lower extremities of Peruvian skeleton from Mochica culture (200 A.D.–800 A.D.). The distal portions of the femurs are widened in an Erlenmeyer-flask deformity. There is similar widening at both ends of the tibias. The pubic and ischial bones are also enlarged. The modeling defects are bilaterally symmetrical.

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with thinning of the cortex and an inverted Erlenmeyer-flask deformity. The involved portion of the bone was of increased lucency and the shaft was bowed laterally (Fig. 2). Both femurs were splayed in their distal parts. The cortices in the widened areas were thinned and the trabeculae were delicate and without a normal stress pattern. Just above the splayed areas, the shafts approached a more normal caliber and the cortices were thickened and surrounded narrow medullary cavities, which were considerably diminished in length. There was increased lucency of the widened areas (Fig. 3 and 4). The tibias showed splaying at both ends with S-shaped bowing, thinned cortices and increased lucency in the widened areas. The



FIG. 2. The humerus is bowed laterally. The upper two-thirds of the bone is widened. A narrow short medullary cavity is surrounded by thickened cortex in the lower third of the shaft. The trabecular markings in the splayed portion are delicate in appearance and without a normal pattern. The modeling defect is greatest in the proximal part of the bone where there is maximal growth.

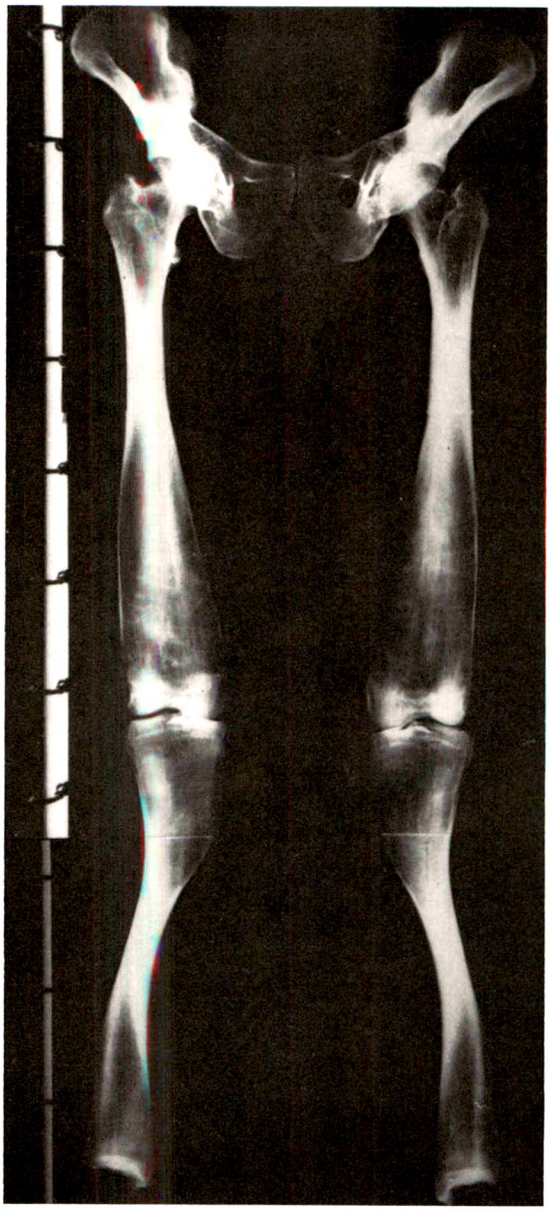


FIG. 3. Roentgenogram of lower skeleton shown in Figure 1. The distal halves of both femurs are splayed. The cortices in the widened areas are thin. There are short narrow medullary cavities surrounded by thickened cortices above the splayed areas. There is S-shaped bowing of the tibias with splaying at both ends. Short narrow medullary cavities surrounded by thickened cortices are noted in the mid-portions of both bones. The modeling defects are bilaterally symmetrical and are most pronounced at the sites of greatest growth potential (lower ends of femurs and upper ends of tibias). The pubic and ischial bones are widened and show thin cortices and increased lucency.

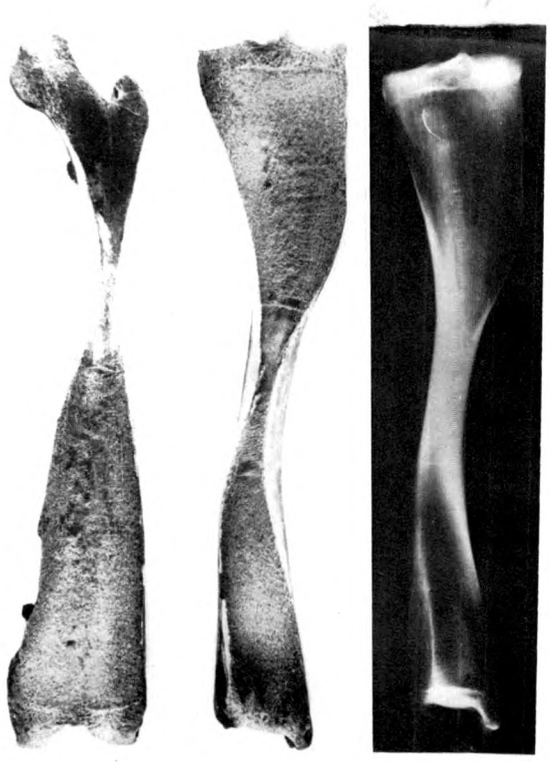


FIG. 4. Sections made through femur and tibia. There are enormous amounts of cancellous bone in the femur above and below a short medullary cavity. There is no funnelization of the distal metaphyseal area, the site of maximal growth. Presumably failure of absorption of the secondary spongiosa has resulted in the persistence of excess cancellous bone, failure to form a normal medullary space and lack of internal remodeling of the spongiosa in response to stress and weight bearing. The cortices in the splayed areas are extremely thin. Similar changes are noted in the tibia. To the right of the figure is a roentgenogram made of the tibia before section.

cortices in their mid-portions were thickened at the level of narrowed short medullary cavities (Fig. 3 and 4). The pubic and ischial bones were widened, and cortical thinning and a delicate trabecular pattern similar to that seen in the long bones were apparent (Fig. 3).

Gross sections of a tibia and a femur showed an overabundance of cancellous bone and short narrow medullary cavities surrounded by thickened cortices. A normal trabecular pattern was not seen (Fig. 4 and 5). The cortices were extremely thin in the splayed metaphyseal regions.

The roentgen and pathologic findings conformed classically to those of craniometaphyseal dysplasia (Pyle's disease). This generalized bone dysplasia, rare in the population of today, was first clinically recognized by Pyle[9] in 1931. Ingalls[5] has suggested that perhaps the original description of this condition was that given by Smith and Jones[12] in 1910 when they described a femur and tibia found in an archaic Nubian cemetery at Dehmit. The lower half of the left femur and the upper half of the left tibia were reported to have been greatly enlarged and thickened without involvement of the knee joint. These findings were apparently unilateral, however, and without further evidence of generalized involvement it is hazardous to accept them as truly representative of cranio-

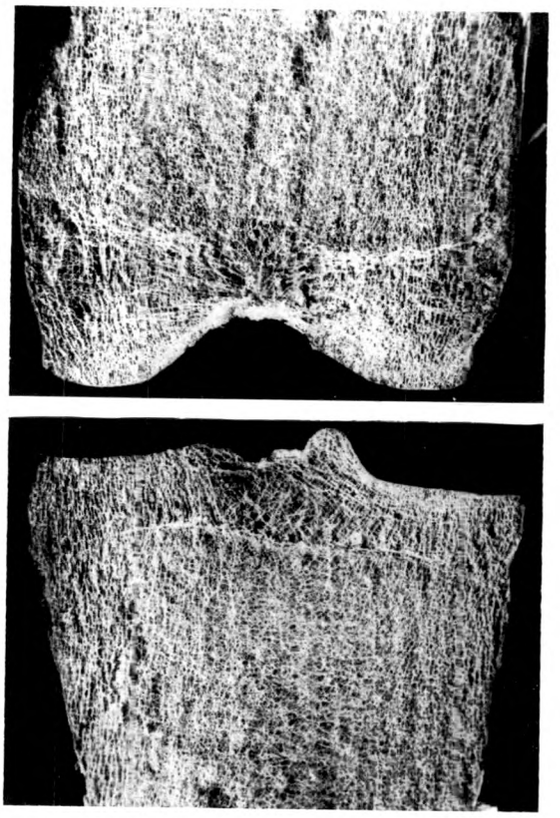


FIG. 5. Detail of distal femur and proximal tibia shows excess spongiosa without normal trabecular pattern. The cortices are extremely thin.

metaphyseal dysplasia. Bakwin and Krida[1] reported findings similar to those of Pyle in a sibling of Pyle's patient in 1937 and other reports[2,4,6,7,10] have documented the condition as a definite clinical entity. For some time, the name familial metaphyseal dysplasia was applied to this entity but the more recent reports emphasizing the cranial manifestations have led to the newer designation of craniometaphyseal dysplasia.

Rubin[11] has classified this disorder as one due to failure of absorption of the secondary spongiosa. The normal reduction in caliber of the shaft is accomplished by internal and external absorption. When these processes fail, normal funnelization of the metaphyses does not occur and the metaphyses appear widened or expanded because all bone formed as a result of endochondral bone formation persists. In such an instance, failure of funnelization becomes more pronounced as a tubular bone grows and is most apparent in those bones with the greatest growth potential. Thus, in craniometaphyseal dysplasia the femur, humerus, tibia and radius tend to show the most widening (amplification). The modeling defect is greatest at that portion of a bone where there is the most growth (polarity). The factors of amplification and polarity, so well described by Rubin, are clearly demonstrated in this ancient skeleton. The humerus is markedly affected and the failure of funnelization is greatest in its upper portion, since humeral growth is maximal at its proximal end. The femurs show advanced modeling defects in their distal parts and the tibias in their proximal portions, sites of greatest growth in these bones.

There are very few descriptions of the gross pathology of this entity. The only autopsy report is that provided by Halliday.[3] His descriptions are focused mainly on the skull and clavicles. The pathology of the long bones is not included. Ingalls[5] reporting on a specimen from Hamann's collection in 1933, described the gross pathology of an affected femur. The condition was an enigma to him at that time but his description of the gross changes in a long bone are corroborated by the findings in this Peruvian skeleton and tend to support Rubin's hypothesis that the basic defect in this dysplasia is failure of absorption of the secondary spongiosa. He reported that the most striking feature of the sectioned long bone is an enormous amount of cancellous bone and an abnormally small and short medullary cavity. He described thickening of the cortex at the level of the medullary cavity and marked thinning of the cortex in the widened metaphyseal segments. Rubin[11] has emphasized that internal remodeling of unabsorbed secondary spongiosa does not occur in this dysplasia. Normally, the trabeculae in the shafts reform as a functional adaptation to lines of force and weight bearing (Wolf's law). In Ingalls' case and in this case, sections of long bones do not show a normal trabecular pattern, presumably because of a failure of absorption and remodeling of the secondary spongiosa of the metaphyses.

The cranial changes have been described in several reports,[3,7,8,11] and are characterized by various degrees of diffuse symmetrical hyperostosis of the vault and base with associated hypertelorism and, frequently, retarded or absent pneumatization of the paranasal sinuses and mastoids.

SUMMARY

Part of a skeleton recovered from an ancient cemetery in the Chicama valley of northern Perú is described. The cemetery and its artifacts have been archeologically identified as those of the Mochica culture which existed between 200 A.D. and 800 A.D.

On roentgenographic and gross pathologic examination, the skeletal parts showed evidence of classic craniometaphyseal dysplasia. The skull was not recovered. The sectioned bone contained an overabundance of normal cancellous bone within the area of which there is no formation of a medullary space. These findings support Rubin's hypothesis that this dys-

plasia is due to failure of resorption of the secondary spongiosa.

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VOL. 99, NO. 3

PYCNODYSOSTOSIS

REPORT OF THREE NEW CASES

By JAMES F. DUSENBERRY, JR., M.D., *and* JOHN J. KANE, M.D.
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PYCNODYSOSTOSIS is a term coined by Maroteaux and Lamy[7] to describe a disease complex which combines some of the features of cleidocranial dysostosis along with osteopetrosis and is characterized by short stature, separated cranial sutures, open fontanels, loss of mandibular angle, dysplasia of the skull bones, partial aplasia of the terminal phalanges, dense bones, and frequent fractures. A review of the literature reveals 30 cases that meet the criteria for pycnodysostosis.[1,4,5,7,11,12,13] The purpose of the authors is to add 3 additional cases to the literature and to list 2 additional findings.

REPORT OF CASES

CASE I. This patient, a 22 year old Negro female, was followed in our Out-Patient Obstetrical Clinic because of an earlier miscarriage at 2 months' gestation. As she was quite short in stature, $4\frac{1}{2}$ feet (Fig. 1, *A* and *B*), she underwent pelvimetry examination which revealed cephalopelvic disproportion. She gave birth to a normal infant by cesarean section after which she developed postpartum psychosis. This gave us an opportunity to study her further and to do blood chemistry studies, all of which were normal. The patient was of normal mentality initially and returned to a normal state shortly after her postpartum psychosis.

The patient's past history was significant in that she reported over 50 fractures. Correspondence with her family physician established that she had "nearer to 100 fractures."

The patient stated that only 1 other member of her family was of her general configuration (Case II).

CASE II. This 28 year old Negro female, a sister of Case I, was found to be normal except for the physical features and the roentgenologic findings of pycnodysostosis. Her medical history is of significance only in that she was seen on numerous occasions for multiple fractures.

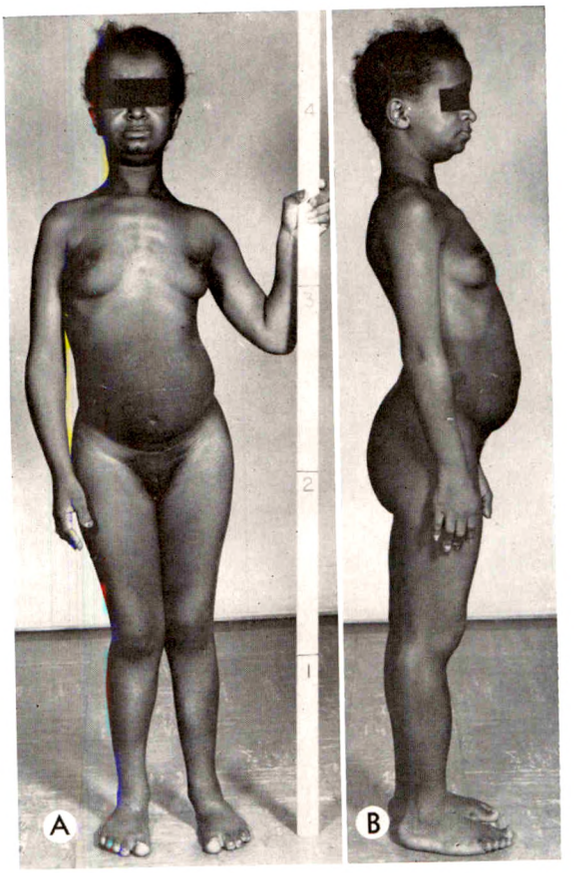


FIG. 1. Case I. (*A* and *B*) The patient is approximately $4\frac{1}{2}$ feet tall. Secondary to the patient being 2 weeks post partum are the protuberant abdomen and the lack of pubic hair. There is bossing of the frontal bones, short stubby wrinkled fingers and toes, with spooning of the nails of the hands and feet.

CASE III. This 38 year old Negro female was referred to us by another hospital, some 150 miles from where Cases I and II lived, for evaluation of osteopetrosis. Insofar as is known, no relationship exists between this patient and Cases I and II. This patient was admitted to her local hospital because of fractures. Physical examination showed that, except for her habitus of pycnodysostosis, she was within normal limits. Blood studies were also normal. Her

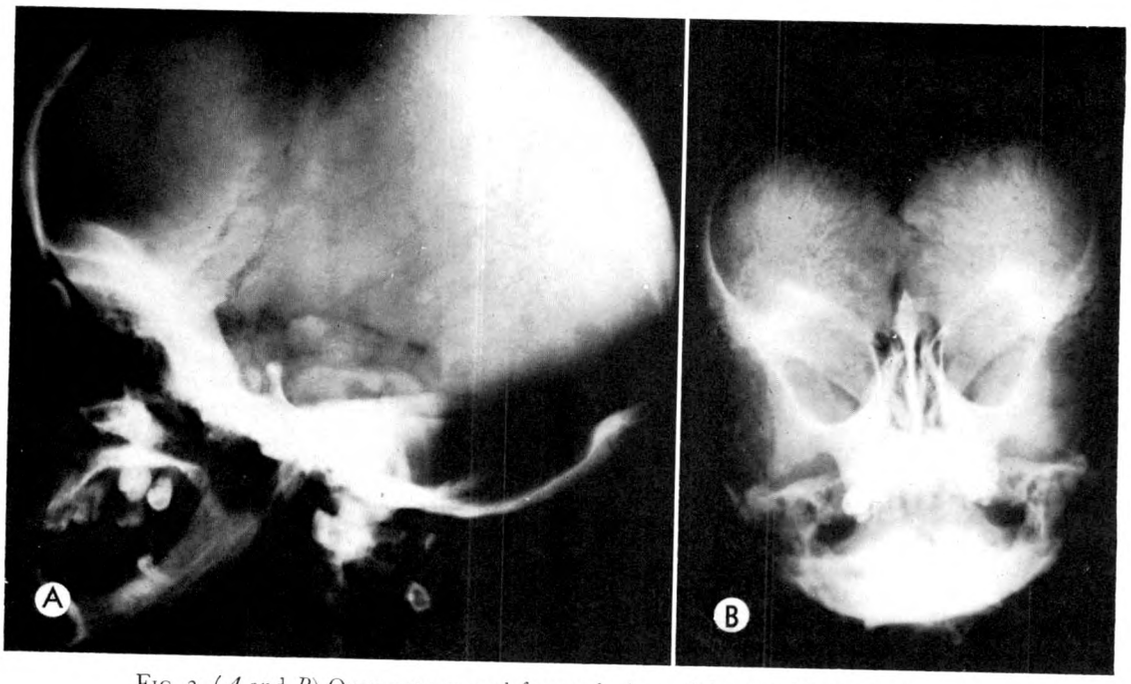


FIG. 2. (*A* and *B*) Open sutures and fontanels, loss of the mandibular angle, and hypoplasia of the facial bones with no aerated paranasal sinuses.

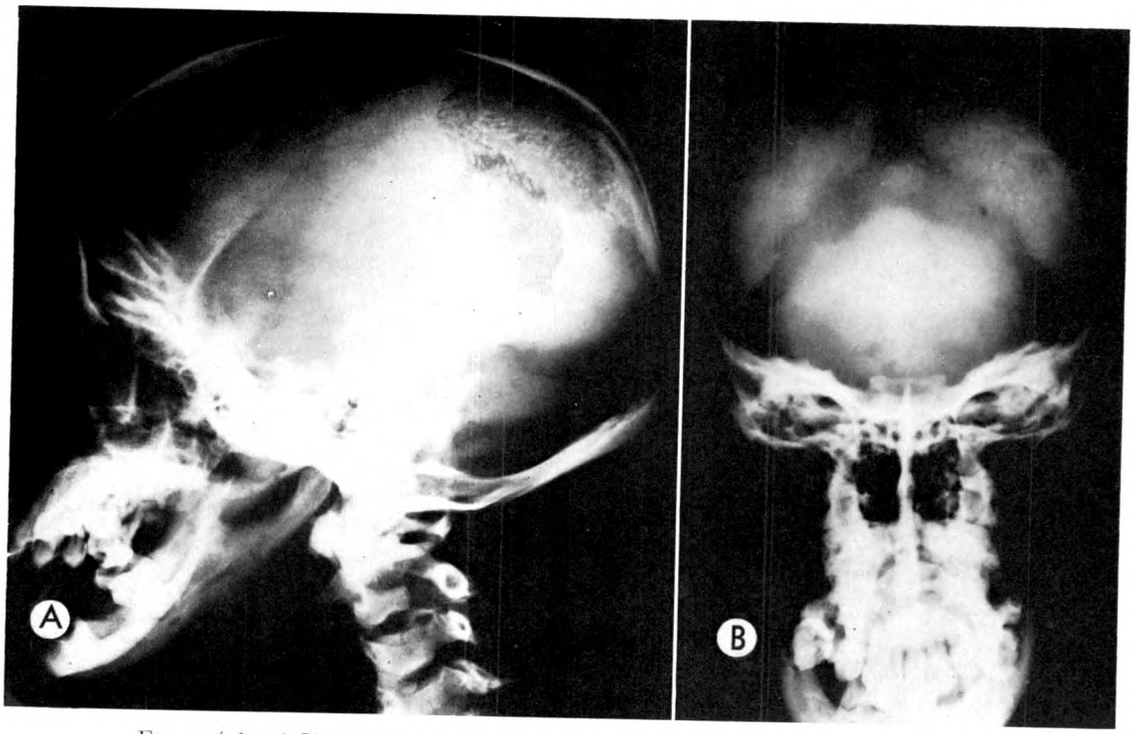


FIG. 3. (*A* and *B*) Roentgenograms show same findings as in Figure 2, *A* and *B*, except that the fontanels are not open.



FIG. 4. The tubular bones are long and thin. The radius is bowed secondary to overgrowth and results in a deformed joint at the wrist. The bones are dense.

roentgenologic findings were those of pycnodysostosis.

DISCUSSION

The most frequent cause for our 3 cases to seek medical treatment was fractures. A review of the literature shows that patients with pycnodysostosis frequently sustain fractures. However, Blasi cited by Maro-

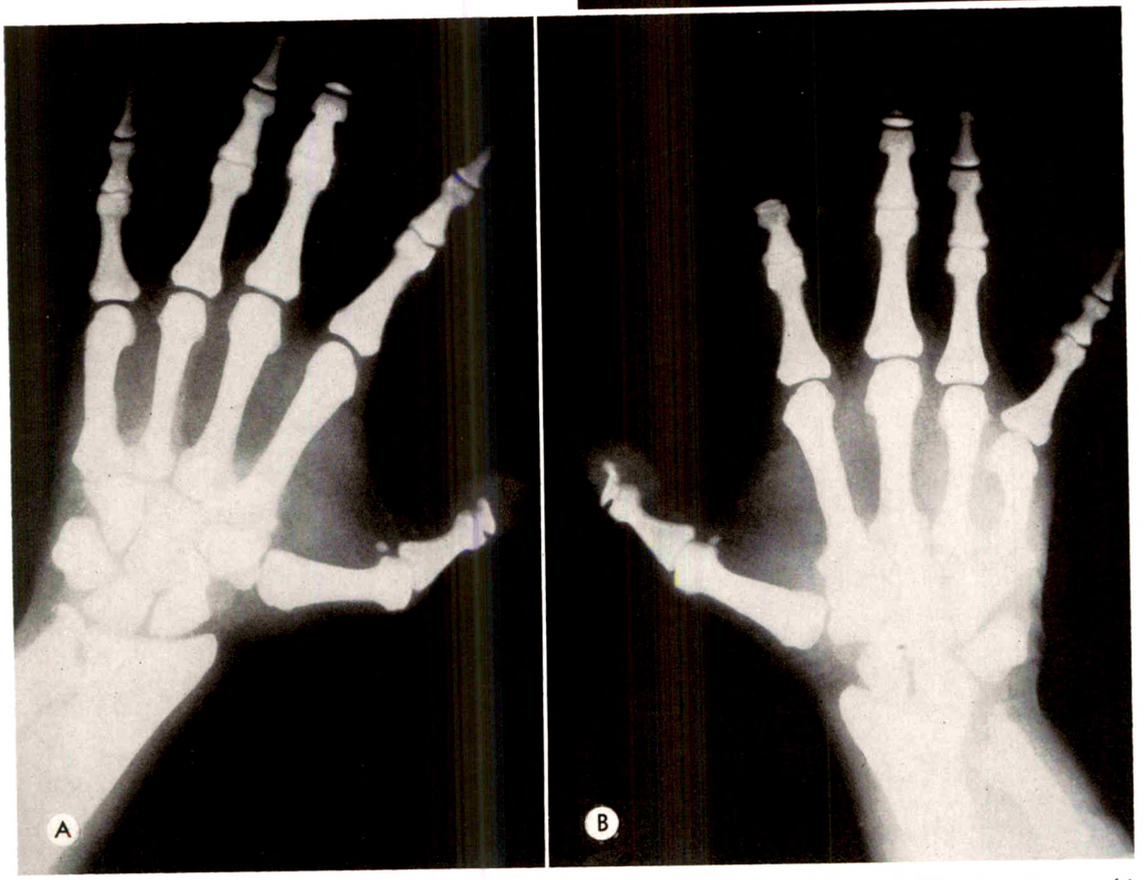


FIG. 5. (*A* and *B*) The hands are short. The shortening of the 5th metacarpal is probably related to an old fracture. The digits which have the distal phalanx intact appear to be tapered; however, those digits which do not have an adequate distal phalanx show aplasia of the ungual tufts and shafts. There is a deformity of the joint space between the radius, ulna and carpal bones secondary to overgrowth of the radius. The bones are quite dense.

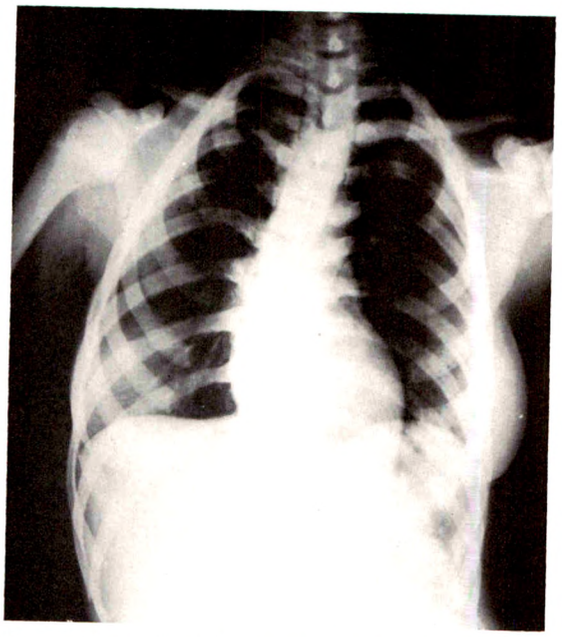


FIG. 6. Generalized increased density of the bones. Note the conical appearance of the chest. The clavicles are intact.

teaux and Lamy[7] and Shuler[11] reported that there was no unusual fragility in his cases.

Maroteaux and Lamy[7] state that this disease is autosomal recessive, as do Elmore *et al.*,[2] and that there is at least a 20 per cent factor of consanguinity. For a discussion of the chromosomal pattern, the reader is referred to the article by Elmore *et al.*[2]

Our study and a review of the literature shows that blood chemistries are normal in these patients. They are characteristically short of stature, generally between $4\frac{1}{2}$ and 5 feet tall. There is hypoplasia of the facial bones which usually causes unattractive features, as well as bossing of the frontal bones. The hands and feet are short and stubby with wrinkled phalanges and spooning of the nails (Fig. 1, *A* and *B*). Any deformities of the extremities can usually be related to previous fractures.

It has been reported that mental retardation is not a characteristic of the disease.[7] Toulouse-Latrec, thought by Maroteaux and Lamy[9] to have pycnodysostosis, is an example of the artistic heights to which these people may rise. Only 2 of the 33 cases of pycnodysostosis have been reported to have mental retardation.[4,12] This may or may not be significant. It must be remembered that the open fontanels leave the brain exposed to trauma.

Sex distribution is equal, the disease having been seen in 18 males and 15 females. Ethnic origin is equally of no apparent significance as it has been reported in Caucasians, Negroes, and Occidentals.[1,4,5,7,11,12,13]

ROENTGENOLOGIC FINDINGS

The most striking feature of this disease is that of generalized osteopetrosis. The bones of the skull (Fig. 2, *A* and *B*; and 3, *A* and *B*) bear the most distinguishing hall-

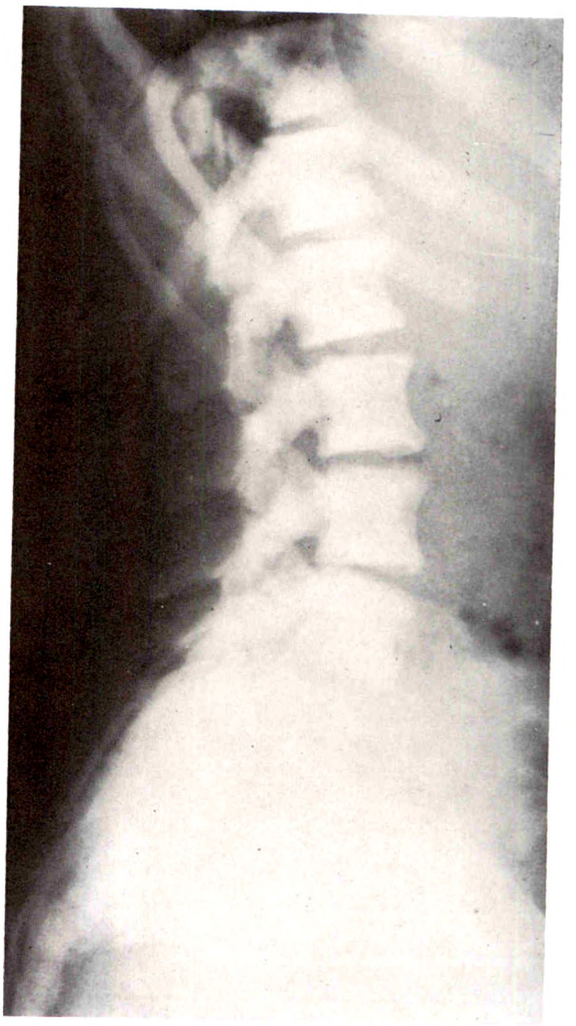


FIG. 7. Dense spool shaped vertebrae.

marks of the disease. These are: flat angles of the mandible, open fontanels, failure of closure of the major sutures, lack of development of paranasal sinuses, and hypoplasia of the maxillary bones with no aeration of the sinuses. There is poor dentition with caries, and frequently there are double rows of teeth. It has not been previously reported that the paranasal sinuses are absent, probably because most studies that have been reviewed by us in the literature have been in children. In our cases, which were adults, there were no aerated paranasal sinuses.

The long bones are thin, delicate, and tubular, provided that they have not been fractured. The radius shows bowing secondary to overgrowth with a resultant abnormal joint at the wrist (Fig. 4; 5, *A* and *B*; and 9, *A* and *B*).



Fig. 8. Generalized increase in bone density. There is bilateral coxa valga. Note that the acetabular angles are increased in relationship to the perpendicular plane. The acetabular fossae are shallow when compared to normal. There is a fracture of the ischium just inferior to the right acetabular fossa and there are old healed fractures of both femurs.



Fig. 9. (*A* and *B*) Generalized increase in bone density, with overgrowth and bowing of the radius. Note the abnormal joint between the radius, ulna and carpals. The transverse fracture of the ulna is typical of fractures seen in pycnodysostosis.

The hands are short and most frequently are described as having tapered phalanges, although this was not present in all of our cases due to lack of ungual tuft development (Fig. 5, *A* and *B*). The feet are quite similar.

The chest appears to be narrow and basically conical. We noted nothing unusual in the clavicles (Fig. 6).

The spine shows the typical vertebrae of osteopetrosis regardless of cause, *i.e.*, anterior notching or spool shaped vertebrae (Fig. 7).

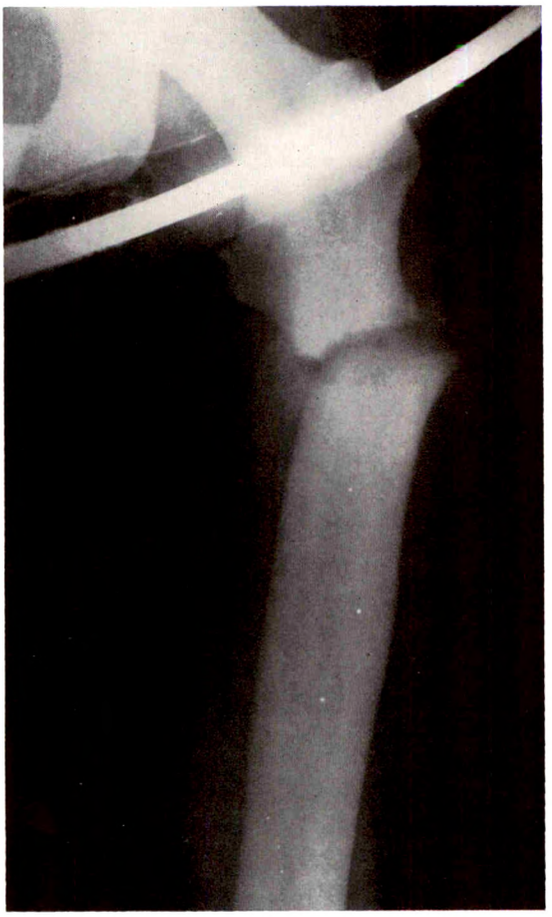


FIG. 10. Osteopetrosis and a transverse fracture of the femur. Such fractures are typical of those seen in pycnodysostosis.

The pelvis often shows coxa valga and shallow acetabula with an increase in the angulation of the acetabula in relationship to the perpendicular plane of the body (Fig. 8 and 10). This latter finding has not been previously reported; however, a review of the literature substantiated its presence.

The fractures are transverse in a manner that is peculiar to a column of marble or the lead of a mechanical pencil, when broken. This is not unlike the snapping of a dry twig. These fractures do heal but quite slowly (Fig. 8; 9, *A* and *B*; and 10).

HISTOLOGY

Elmore and Hillman[1] and Shuler[11] have reported bone biopsies. Shuler stated that his patients had abnormally dense cortical bone with very small haversian canals. From his specimen, he was unable to say whether this differed from osteopetrosis, in general, or was a variant. Elmore and Hillman reported that persisting mineralized osteochondroid filled the potential marrow space. Coarse fiber bone was formed as well as primitive haversian systems. The cement lines were wide. The general pattern of the bone formation was one of structural and cellular disorganization and failure to remodel primitive elements. They believe that this results in a loss of bone strength and, therefore, frequent fractures.

SUMMARY

Three cases of pycnodysostosis are reported.

Each presented the characteristic features of the disease. These are: shortness of stature, osteopetrosis, open fontanels or sutures or both, marked decrease in angulation of the mandible, absent paranasal sinuses, bone fragility, short stubby hands and feet, coxa valga, and shallow acetabula with increased angulation. The blood studies were normal.

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AN UNUSUAL CASE OF BRACHYDACTYLY*

PERIPHERAL DYSOSTOSIS? PSEUDO-PSEUDO-HYPOPARATHYROIDISM? CONE EPIPHYSES?

By RICHARD ARKLESS, M.D., *and* C. BENJAMIN GRAHAM, M.D.†
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A WOMAN with brachydactyly of her hands and feet was referred for treatment of endometrial carcinoma. She carried a diagnosis of pseudo-pseudo-hypoparathyroidism, and, initially unknown to us, her case had been reported in the literature under this same title by Miles and Elrick.[29] The patient's osseous abnormalities are reviewed here in light of some additional and somewhat differing genetic, physical, and roentgenographic findings and because of the availability of more recent information about pseudo-pseudo-hypoparathyroidism and other possibly related conditions, including peripheral dysostosis, cone epiphyses, and achondroplasia.

REPORT OF A CASE

C.B., a 37 year old white female under treatment for endometrial carcinoma, was born at home in Denver, Colorado. There were no seizures in childhood, but she had two "blackout spells" at the ages of 5 and 8 years. Schooling was meager; however, she can read and write. Subsequent to a fall, there occurred voluntarily correctable outward deviation of the left eye. Apparently because of low mentality, she was institutionalized from the ages of 12 to 18 years. Menses began at the age of 13 years, were of small quantity, lasted 2 to 3 days, and ranged in frequency from every 1 to 2 months to 1 to 2 times per year. She was amenorrheic for 14 months 5 years ago. Although briefly married in 1950 and again married for the last 3 years, she has had no children.

There were no full siblings, but an unknown number of maternal and 8 paternal half-siblings are known to exist. Her father and 3 brothers were said to have "unusual thumbs." Hand roentgenograms of one of them demonstrated a short terminal phalanx of one thumb; the remainder of a limited skeletal survey was negative, however. Two siblings had cleft lips. There is no familial history of seizures or cataracts. Heights range from a 5 foot 2 inch sister to a 6 foot brother.

Our patient's measurements were: height $58\frac{1}{2}$ inches, weight 220 pounds, armspan $53\frac{1}{2}$ inches, upper arm length $11\frac{1}{2}$ inches, and forearm length $9\frac{1}{2}$ inches. Blood pressure was normal. There was mild ocular hypertelorism and a voluntarily correctable external deviation of the left eye, but no lens or corneal abnormalities. Webbed neck and low hair line were absent. Normal teeth, ears, thyroid, breasts, heart, lungs, and abdomen were noted, and neurologic studies were normal. Endometrial carcinoma was found by biopsy. Hands and feet were short. Nails were short but otherwise normal. Normal values were obtained for serum calcium (10.0–10.9 mg./100 ml.), phosphate (3.6–4.1), alkaline phosphatase, serum proteins, and liver function studies. The electrocardiogram and urinalysis were normal, and the serology was negative.

Roentgen Findings. Roentgenograms of the hands (Fig. 1, *A* and *B*) showed almost universal brachymetacarpy and brachyphalangy. There were small bony protuberances on the ends of several metacarpals. Heart-shaped notches on the proximal articular surfaces of multiple proximal phalanges were noted, with all involved phalanges also having distal circumferential indentations (residual changes from prior pseudo-epiphyses?). Similar but less symmetric notching was found on several of the middle phalanges proximally. The distal phalanges were short. The few uninvolved bones were virtually normal in size and shape. Secondary degenerative changes were present throughout.

The feet (Fig. 2, *A* and *B*) demonstrated metatarsus varus and brevis. There was brachymetatarsy with relative sparing of the left fifth and both second toes. Bony protuberances were noted in several areas. Universal brachy-

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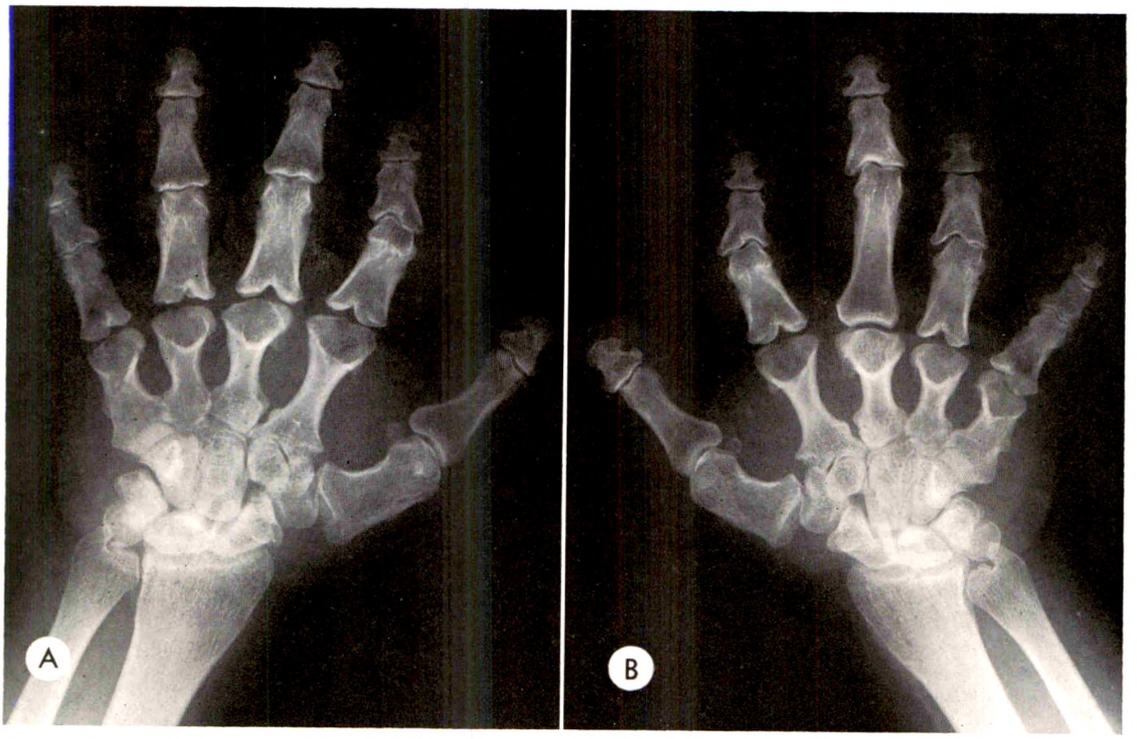


Fig. 1. (*A* and *B*) Roentgenograms of the hands show brachymetacarpy and brachyphalangy, with small bony protuberances on the ends of several metacarpals; heart-shaped notches on the proximal articular surfaces of multiple proximal phalanges and some middle phalanges; and marked shortening of the distal phalanges. Secondary degenerative changes are present throughout.

phalangy was present. Fusion of both fifth distal interphalangeal joints was noted. Epiphyseal indentations dissimilar from those in the hands, as well as secondary degenerative changes, were seen.

The pelvis and lumbosacral spine (Fig. 3; and 4, *A* and *B*) showed narrowing of the interpedicular distances in a craniocaudal direction with decreased pedicle height inferiorly. There were shortened valgus femoral necks and flared iliac crests, but normal disk spaces and sciatic notches. Roentgenograms of the thoracic spine (Fig. 5, *A* and *B*) revealed only vertebral plate irregularities.

Roentgenograms of the skull (Fig. 6, *A* and *B*) showed ocular hypertelorism but no basal ganglia calcification or sellar abnormality. Skull configuration and thickness were normal. The cervical spine, including the odontoid, was normal. The ankles and knees (Fig. 7; and 8, *A* and *B*) were likewise normal. The elbows and shoulders (Fig. 9; and 10) revealed dorsal bulges of the proximal ulnae and slight underdevelopment of the glenoids.

No soft tissue calcifications were noted.

Discussion

The diffuse bone changes in this patient are most pronounced in the peripheral portions of the appendicular skeleton. They will be discussed in reference to several conditions, including pseudo-hypoparathyroidism, pseudo-pseudo-hypoparathyroidism, achondroplasia, cone-shaped epiphyses, peripheral dysostosis, Thiemann's disease, and Kashim-Beck disease.

Pseudo-hypoparathyroidism and pseudo-pseudo-hypoparathyroidism

In 1942, Albright *et al.*[1] described 3 patients with pseudo-hypoparathyroidism (PH), a condition in which parathormone target organs are apparently unresponsive. Hypocalcemia and hyperphosphatemia occur. No hand roentgenograms were shown, but the photograph of one hand revealed brachydactyly. Eight years later, in describing 4 new cases and in reviewing their prior ones as well as 7 of other authors, this

group stressed the frequent occurrence of the unusual type of brachydactyly found here.[16] They also delineated most of the other features which today are generally considered to be a part of the syndrome (see below). Subsequent reports have shown that, with the very frequent exception of the index finger, any of the metacarpals can be shortened. Different patients have various combinations of fingers involved. Of the 14 cases reported by Albright's group in 1950, 4 had no brachydactyly.

During the next 15 years, there were numerous reports of PH (see reviews by MacGregor and Whitehead[26] and by Mann *et al.*[27]). Studying these, one notes other bone abnormalities upon which emphasis was not always placed. The most frequently seen accessory changes are "stubby" distal phalanges, a short fifth middle phalanx, and articular changes in the hands (see below), with similar changes seen sometimes in the feet.

There is a current tendency to consider anyone with similar appearing hands as a *forme fruste* of PH. This is not necessarily true, because not only are these changes not required for this diagnosis, but similar hand roentgenograms can also be found in otherwise normal people as well as in association with other known diseases. Hochheim[23] in 1903 described 1 such person and Birkenfeld[8] in 1928 reported a family with many similarly affected siblings; both reviewed many cases of brachydactyly in the literature, some of which also had PH-like hands.

Perhaps inevitably, there was born in 1952 the term pseudo-pseudo-hypoparathyroidism (PPH).[2] This was meant to include those people with normal plasma calcium and phosphorus levels who had the same unusual brachydactyly and many

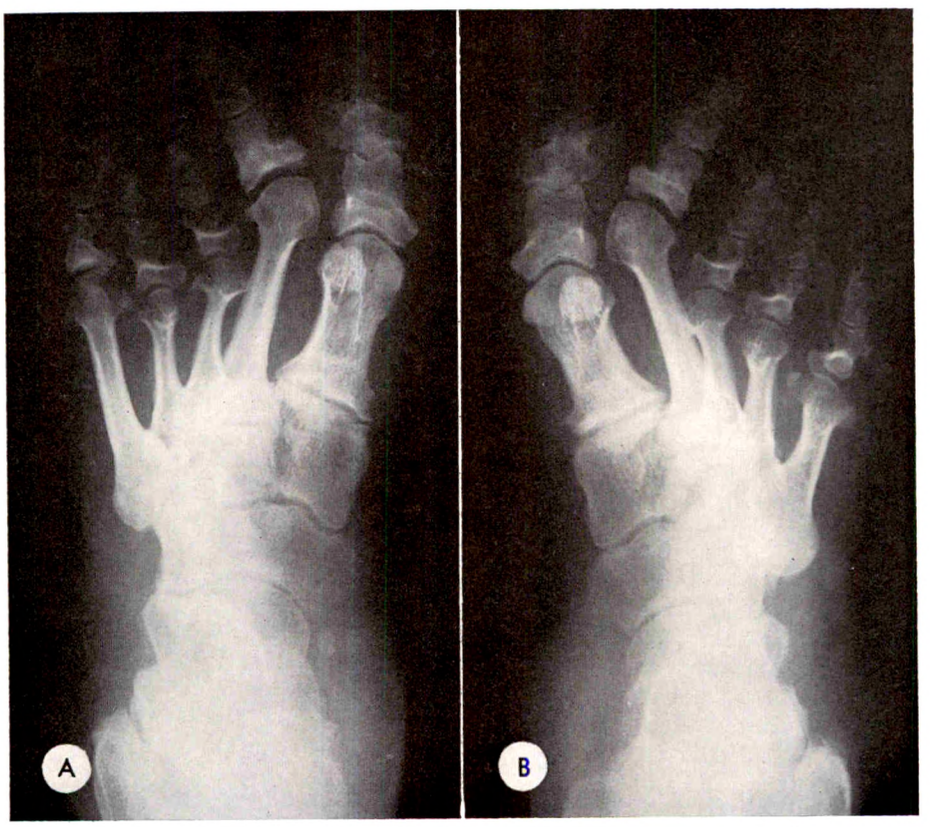


FIG. 2. (*A* and *B*) Roentgenograms of the feet show metatarsus varus and brevis, with bone changes similar to those observed in Figure 1, *A* and *B*.

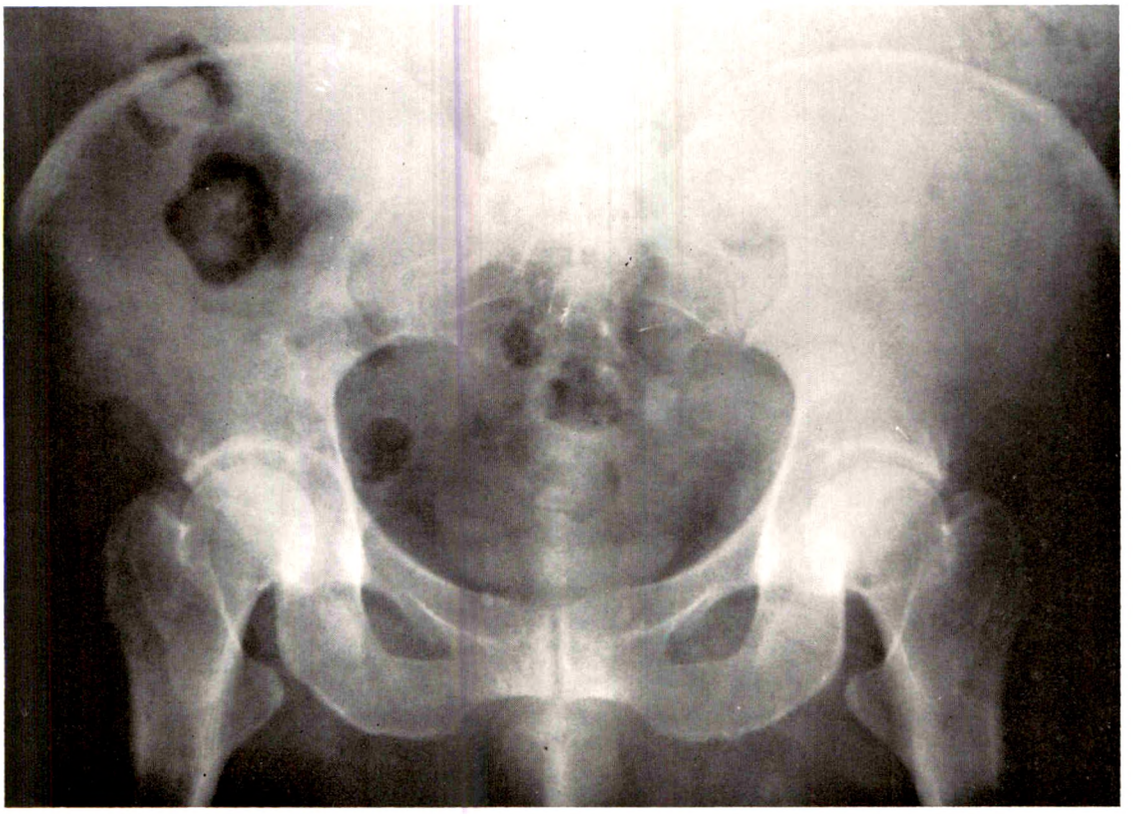


Fig. 3. Roentgenogram of the pelvis shows shortened valgus femoral necks and flared iliac crests.

physical findings similar to patients with PH, including: short stature, obesity, and round facies (each by itself rather nonspecific); basal ganglia calcification (seen also in such unrelated conditions as toxoplasmosis, tuberous sclerosis, idiopathic familial calcification, and secondary to various toxic agents); soft tissue calcifications or ossifications (seen also in collagen diseases, chronic renal disease, Ehlers-Danlos disease, myositis ossificans, etc.); thickened calvarium; lenticular opacities; and occasionally exostoses and delayed appearance of secondary sex characteristics. Albright and co-workers' original case of PPH was a girl, 63 inches in height, with "typical" hand changes and bone in the soft tissues (proved by biopsy) but without basal ganglia calcification.

The term pseudo-pseudo-hypoparathyroidism would seem valid, however, only if there is either a family history of PH or evidence of a transition between PH and PPH. In this regard, Ray and Gardner's case[32] of PPH was later reported by Papadatos and Alivisatos[31] as becoming PH; Palubinskas and Davies' case[30] of PH became one of PPH; McNeeley and coworkers' case of PPH[28] had a low serum calcium on a low calcium diet; and Gershberg and Weseley's case[20] vacillated between PH and PPH. There are also many reports of PH and PPH in different members of a family. It is interesting that relatives of Bille's case of PH[7] had atypical hand abnormalities. Without such evidence, reporting a case of brachydactyly as PPH seems unjustified.

Cases with multiple exostoses have been reported as PPH by several authors, and subsequent studies of inheritance and sex incidence of PH and PPH have been confused by the uncritical inclusion of these cases. However, multiple exostoses alone may involve the phalanges and independently cause brachyphalangy. There are

abundant cases reported as PPH which do not to the present authors resemble PH or PPH as originally described. Whether one desires to consider any of them as representing this syndrome, or as being merely brachydactyly similar to Hochheim's or Birkenfeld's cases, seems mainly a matter of personal preference. Several articles include Brailsford's type of familial brachydactyly[11] in their differential diagnosis, but, because these patients have extremity changes which might be considered as either PPH or Hochheim type brachydactyly and because there are no statements concerning other findings of PH-PPH, clear differentiation is not possible.

Another condition frequently associated with short metacarpals of the type seen in PH is Turner's ovarian agenesis. The classic change here is the "metacarpal sign," where the fourth metacarpal does not quite reach a line drawn between the distal ends of the third and fifth metacarpals. Occasionally, the fourth or other metacarpals are extremely short. To diagnose such cases of Turner's syndrome as having concomitant PPH[17,24,42] on this basis seems unjustified. Were one to do this, one should also include some cases of osteopetrosis,[25] "chondrodystrophy,"[36] myositis ossificans progressiva,[33] and others as also having PPH. Myositis ossificans has been discussed as being related to PH-PPH.[16,27] The presence of a rather unrelated type of

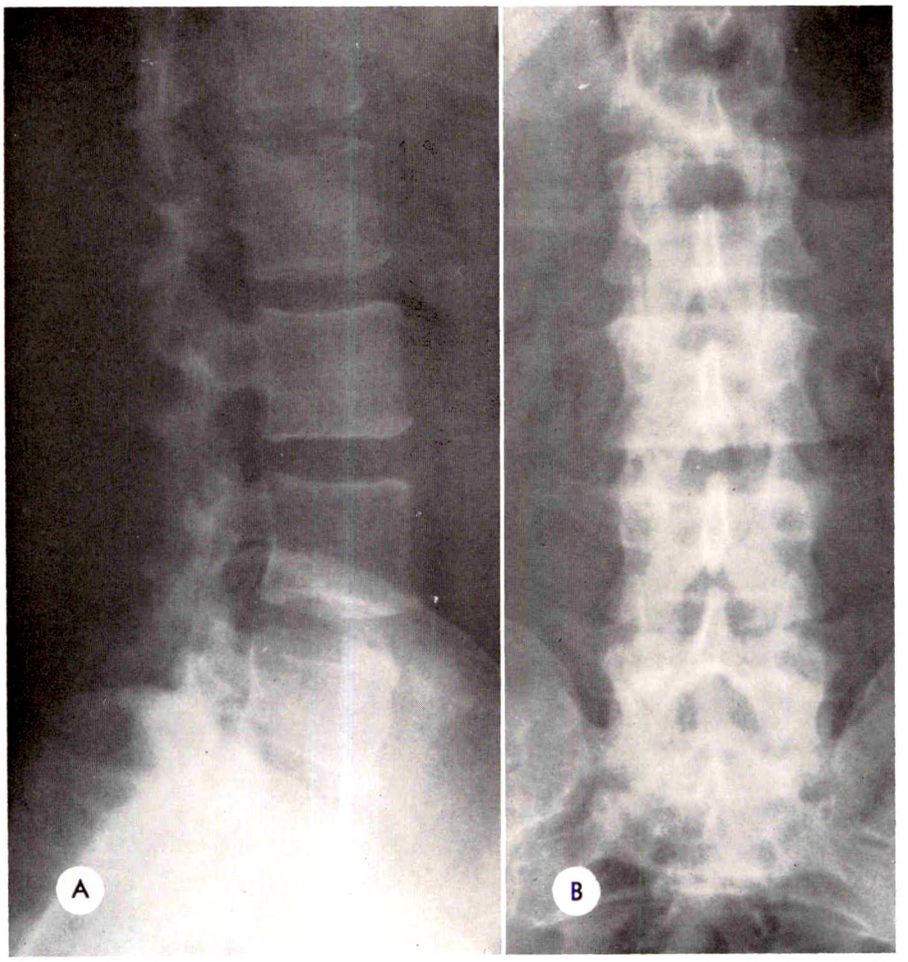


Fig. 4. (*A* and *B*) Roentgenograms of the lumbosacral spine in lateral and anteroposterior projection demonstrate narrowing of the interpedicular distances in a craniocaudal direction with decreased pedicle height inferiorly. There are normal disk spaces and sciatic notches.

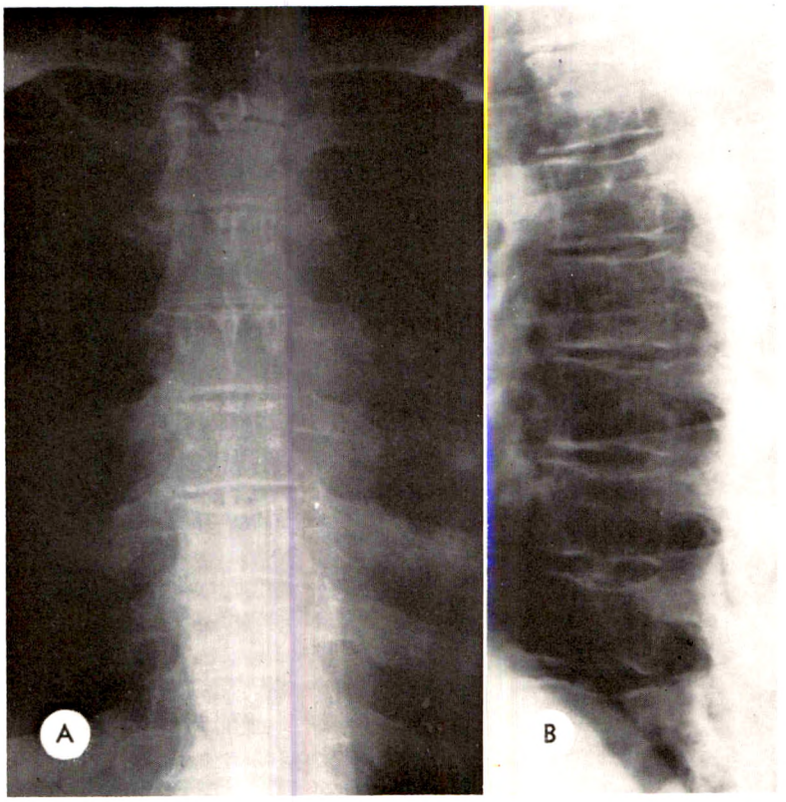


Fig. 5. (*A* and *B*) Roentgenograms of the thoracic spine show vertebral plate irregularities.

brachydactyly and a different distribution of bone deposits in soft tissues seem to emphasize dissimilarities, however. There are many other types of brachydactyly and these also appear to have no relation to PPH.

Is our patient a case of PPH? She is short and has "brachydactyly," but these are found in many types of bone dysplasias. She is obese, has a round face, has low intelligence and an irregular menstrual history, but these are *per se* nonspecific. She has neither lenticular opacities (although she apparently did when originally reported[29]) nor intracranial or soft tissue calcifications, nor a thick calvarium. The term pseudo-pseudo-hypoparathyroidism does not seem appropriate.

Peripheral Dysostosis, Cone Epiphyses, and Other Conditions

In 1960, Singleton *et al.*[38] reported 2 cases of peripheral dysostosis in which growth disturbances were most pronounced in the epiphyseal areas of the hands and feet. These were similar to cases described earlier by Brailsford,[10] and resembled, in some aspects, one of the earlier patients with PH described by Elrick *et al.*[16] The epiphyses had the shape of a heart (Fig. 11, type 3b) and the growth plates closed early, resulting in short stubby phalanges whose affected ends had a peculiar notch (Fig. 11, type 5). It is emphasized that the growth disturbance, although most obvious in the hands and feet, was also noted in the slightly shortened distal ulnae, where the major ulnar growth occurs, and in the distal femoral shafts (there was underconstriction in 1 case and overconstriction in the other). The similarity of these cases to ours is apparent. In addition, Singleton (personal communication) has found in all but 1 of several advanced cases now under his observation a decreasing lumbar interpedicular distance in a cephalocaudal direction, a finding seen in our patient as well.

Other reports of this condition have ap-

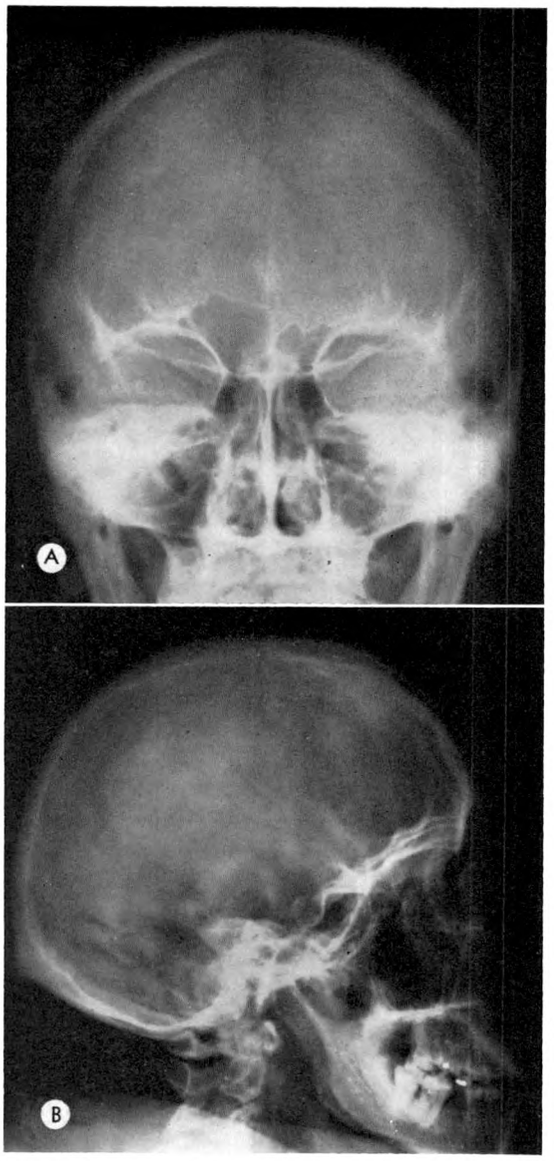


Fig. 6. (*A* and *B*) Roentgenograms of the skull in posteroanterior and lateral projection show ocular hypertelorism. The configuration of the skull and the thickness of the bones are normal. There is no evidence of basal ganglia calcification or sellar abnormality.

peared frequently under other titles. Conversely, some cases called peripheral dysostosis do not appear to be the same condition. This is in part a semantic problem since there seems to be a spectrum ranging through achondroplasia, "hypochondroplasia," PPH, cone epiphyses, and peripheral dysostosis.

In the same year as Singleton's report, Ruffato and Godina[35] reported 4 cases as peripheral dysostosis. In 3, the main roentgenographic findings were epiphyses of either a "cone" or "collar button" type (Fig. 11, type 2a and 2b), and in the fourth there was notching of the fused epiphyses (Fig. 11, type 6). It should be pointed out that epiphyses of types 2a and 2b are not necessarily abnormal, being occasionally seen in the feet of normal children.[44] Also, they have been noted in association with such a variety of conditions as to be, by themselves, of little diagnostic value. These include osteopetrosis,[25] dysplasia epiphysialis hemimelicia,[18] Freiberg's affliction,[19] Apert's acrocephalosyndactyly,[15] gigantism of other phalanges,[13] Marchesani syndrome,[40] chondroectodermal dysplasia,[12] familial brachydactyly,[8] cleidocranial dysostosis,[10] PH,[16] and achondroplasia.

The next year Alé and Caló[3] reported, also under this title, a patient who, in addition to having multiple exostoses, demonstrated a diffuse but mild brachydactyly with cone-shaped phalangeal epiphyses. In



Fig. 7. Roentgenogram of the ankle joint reveals normal appearance.

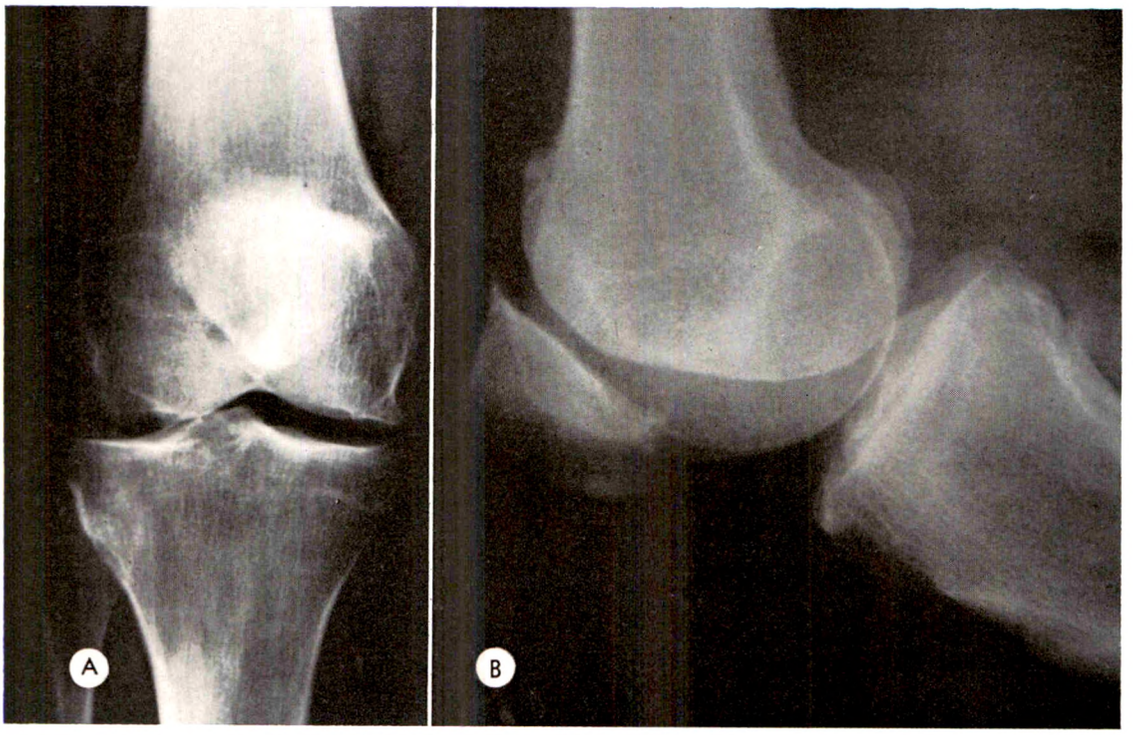


Fig. 8. (*A* and *B*) Roentgenograms of the knee joint in posteroanterior and lateral projection show normal appearance.

this regard, Biedermann's case 4 with multiple exostoses[6] also had a single heart-shaped phalangeal epiphysis (Fig. 11, type 3b).

Concerning the etiology, a local vascular disturbance at the growth plate seems



Fig. 9. Roentgenogram of the elbow in lateral projection demonstrates dorsal bulge of the proximal ulna.



Fig. 10. Roentgenogram of the shoulder shows slight underdevelopment of the glenoid with some irregularity of the bone structure of the proximal humerus.

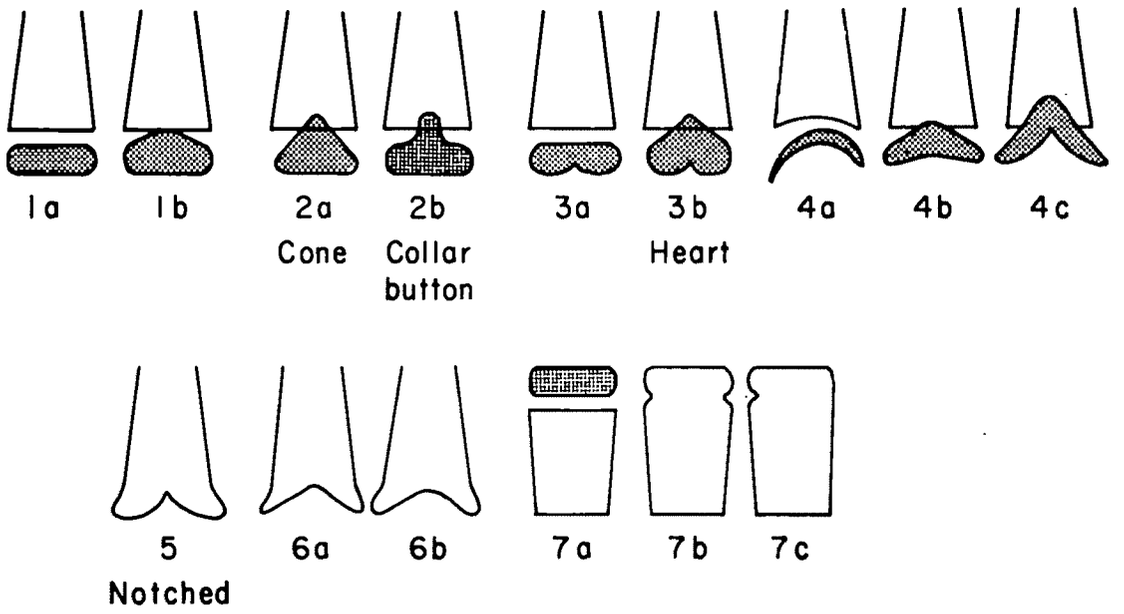


FIG. 11. Diagram illustrating various forms of epiphyses.

likely. It is postulated that the central position of this plate grows the least, while the more peripheral portions, perhaps better nourished by vessels which are of somewhat different origin and course, continue to grow and push the peripheral epiphyseal areas ahead. The result is a conical shaped epiphysis. If the peripheral parts are completely spared, there may be little shortening until premature bone fusion occurs through the abnormal central portion of the growth plate. With increasing degrees of more peripheral vascular compromise, the brachydactyly would become even more evident before closure has occurred. Rubin[34] has presented an excellent discussion in this regard. It is noteworthy that Vaughan's[43] case of peripheral dysostosis also had bilateral Legg-Perthes' disease, a condition thought also to be secondary to vascular embarrassment. The abnormal phalangeal epiphyses in Vaughan's patient were either cone-shaped (Fig. 11, type 2a or 2b) or inverted V shaped (type 4c). Cohen and van Creveld's[14] patient with peripheral dysostosis also had prematurely fusing cone epiphyses, as well as a wide sunken nasal root and premature epiphyseal closure at the elbow. Hobolth and Mune's[22] case had type 4a phalangeal epiphyses.

Prior to Singleton's report, similar epiphyseal abnormalities had been described under various names, including cone epiphyses, "Zapfenepiphysen,"[40] and inverted V-formed epiphyses. These were considered abnormal. However, Venning reviewed this subject and emphasized that these cone-like epiphyses could be a normal variation, at least in the feet, but that they sometimes fused early.[44] Several authors noted the frequent occurrence of pseudo-epiphyses on the ends of the involved phalanges (Fig. 11, type 7b). However, Snodgrasse *et al.*[39] demonstated that such pseudo-epiphyses by themselves can also be a normal variation.

Two unrelated conditions causing phalangeal deformity should be mentioned in the differential diagnosis of notched phalanges and cone epiphyses: Thiemann's disease and Kashim-Beck's disease. The former involves swelling and pain in the metacarpophalangeal and/or interphalangeal joints during adolescence. The etiology is unknown but it is sometimes familial. The end result is a deformity (Fig. 11, type 6b) resembling the notched phalanges discussed above (type 5). Although the two processes are usually distinguishable roentgenologically, there are patients with

typical notched phalanges who have other phalanges resembling Thiemann's disease, a probable result of secondary degenerative changes. Kashim-Beck's disease, usually found in certain parts of Russia and perhaps related to nutritional disturbances, results in varied fragmentations and deformities in peripheral epiphyses, one form of which (Fig. 11, type 4a) is suggestive of notched phalanges.

Although cone epiphyses (Fig. 11, type 2a and 2b) can be a normal variation in the phalanges, in other joints they represent stigmata of various abnormal conditions. They have been observed in the distal femur in hypervitaminosis A,[21] and in healing scurvy,[37] probably secondary to damage in the growth plate. Following distal femoral trauma, 1 patient of Liess, who also had cone epiphyses in hands and feet, developed a similar appearance. A patient of Augustin,[5] also with cone epiphyses in pedal phalanges, had a cone epiphysis in one proximal tibia in which trabeculae were demonstrated bridging the growth plate centrally at the apex of the cone. This patient had a limp since birth. Similarly, transepiphyseal bone grafts, osteomyelitis, and sickle cell anemia can all cause a central epiphyseal growth arrest, and prolonged immobilization for congenital hip dislocation can result in cone-shaped prematurely fused knee epiphyses.[9] Certain congenital bone dysplasias, *e.g.*, diastrophic dwarfism and achondroplasia, are accompanied by similar distal femoral appearances. In other words, there are a limited number of ways in which bone can react to various stresses, and different stresses can result in similar end-stage appearances.

ACHONDROPLASIA

Although the reported patient is not a classic achondroplastic dwarf, she has a few changes reminiscent of that condition in a mild form: the over-all height and limb lengths are short, and the lumbar interpedicular distances diminish cephalocaudally. This latter change is thought to be one of the characteristic findings of achondroplasia; it is found in our patient and, as previously noted, in Singleton's cases of peripheral dysostosis.

SUMMARY

A patient with an unusual type of brachydactyly is described. Although most bones of the hands and feet demonstrated diminished longitudinal growth, there were a few which were normal. Growth disturbances were present in other bones, both in the axial and appendicular areas. Similar cases in the literature described as "peripheral dysostosis" also had, on close inspection, some central growth disturbances.

The patient's bone anomalies are also discussed with reference to so-called "pseudo-pseudo-hypoparathyroidism"; this diagnosis is thought not to be appropriate because there was no personal or familial history to suggest present or prior pseudohypoparathyroidism. There was also no evidence of a familial brachydactyly.

The origin of the shortened phalanges is discussed in relation to the condition called "cone epiphyses," which is in itself not necessarily abnormal.

Our case represents an anomaly which transcends the spectrum of normal variations and finds its place in the limbo of chondro-osseous dysplasias.

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THE HAND AS AN INDICATOR OF GENERALIZED DISEASE

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ROENTGENOGRAMS of the hands often reflect the picture of generalized disease. In evaluating roentgenograms of the hands, the careful analysis of features applicable to bone disease in general should be used. This comprises independent observation of periosteum, cortex, medulla, location of lesion, bone production, or destruction, erosion, resorption and soft tissue changes.

CLASSIFICATION

The predominating pathologic changes of the material presented fall into the following categories: (A) periosteal changes; (B) soft tissue changes; (C) changes in the tufts; (D) changes in the wrists; (E) destructive and lytic changes; and (F) diffuse changes.

DESCRIPTION OF DISEASES BY GROUPS

A. PERIOSTEAL CHANGES

1. *Pulmonary osteoarthropathy.* In severe cases of pulmonary osteoarthropathy, new bone may be seen around the shafts of the

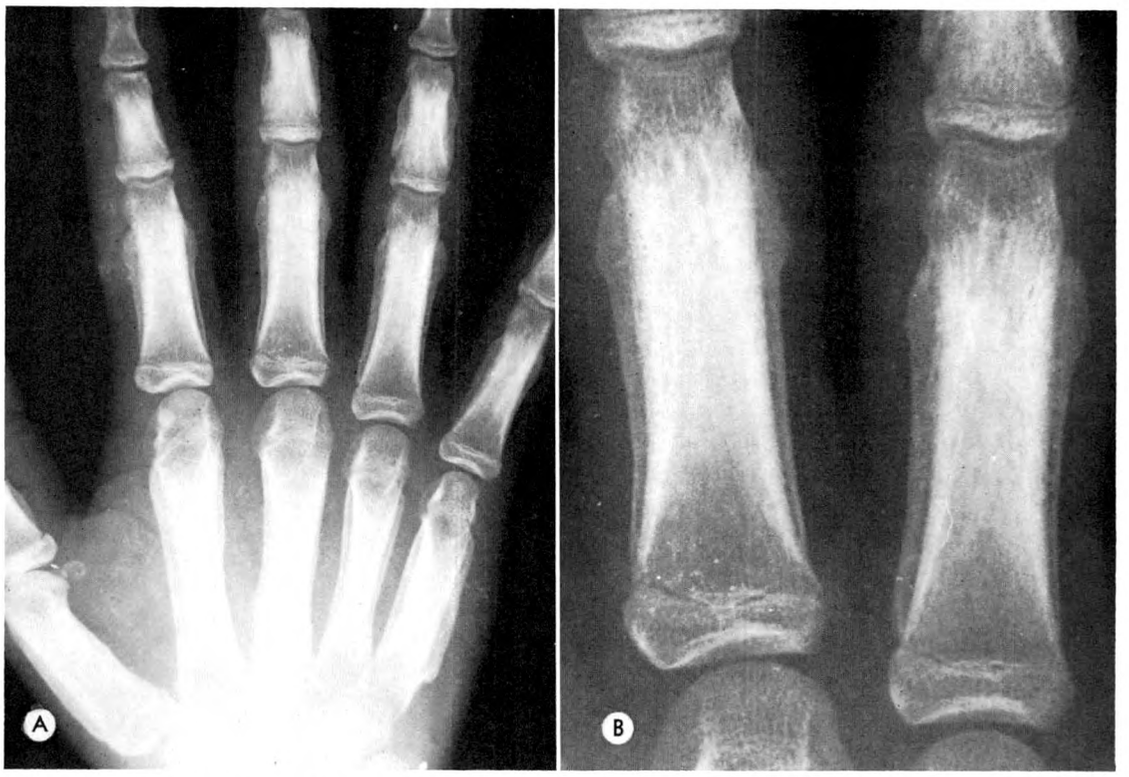


FIG. 1. (*A* and *B*) *Pulmonary hypertrophic osteoarthropathy*, secondary to pulmonary metastases from osteogenic sarcoma. There is longitudinal periosteal new bone formation along the shafts of all metacarpals, proximal and distal phalanges.

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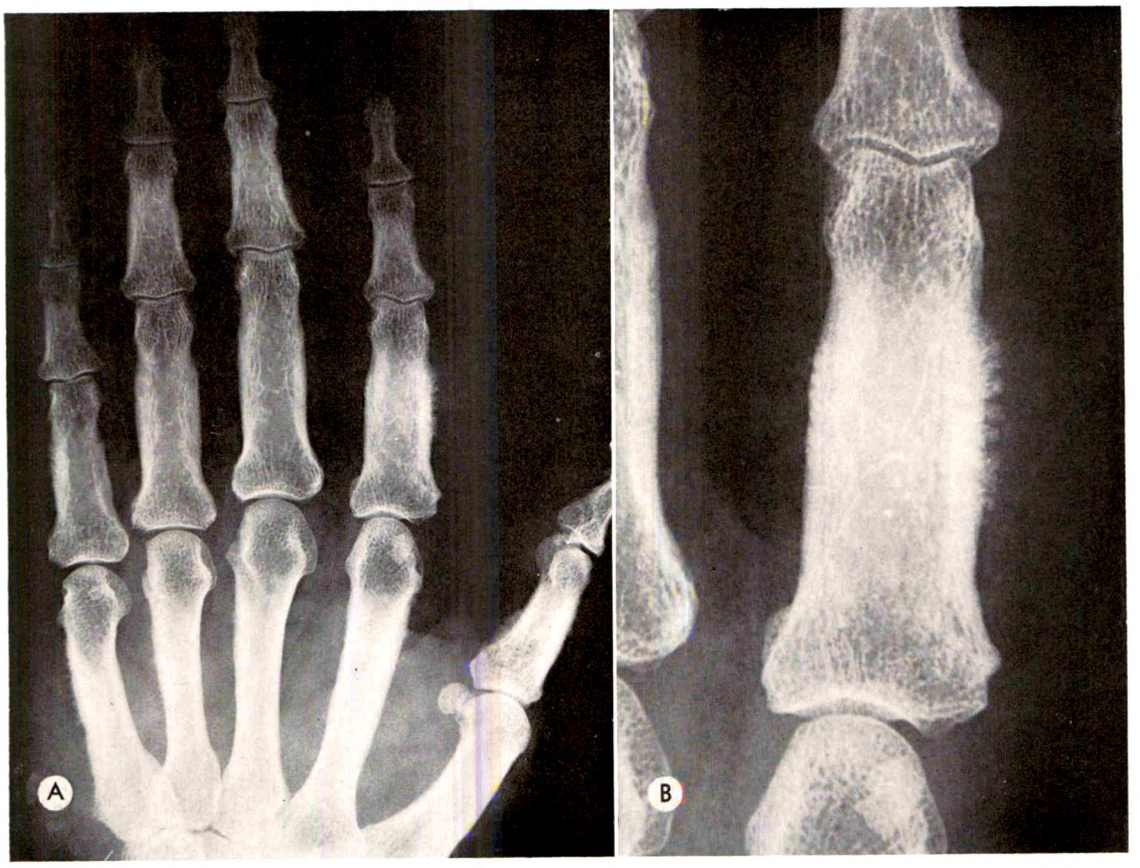


Fig. 2. (*A* and *B*) *Thyroid acropachy*. Periosteal new bone formation with a perpendicular spiculated appearance is present in varying degrees along several metacarpals and phalanges.

metacarpals and metatarsals and, occasionally, around the proximal and middle phalanges. There is usually a narrow translucent line between the periosteal new bone, and the cortex of the bones of both sides of the body are symmetrically involved. Pulmonary osteoarthropathy is associated with joint and bone pain and must be searched for roentgenologically (Fig. 1, *A* and *B*).

2. *Thyroid acropachy*[12,16] is an unusual complication of thyroid disease. About one-half of the patients are euthyroid at the time of onset. The periosteal new bone is characteristically irregular with many small rounded radiolucent areas, giving it a lacy appearance. The distribution of the lesions is typically diaphyseal, being more marked on the mid-portion of the diaphysis, giving the shaft a fusiform contour. The periosteal reaction has a spiculated appearance with the spicules perpendicular to the longitudinal axis of the bone. The involvement of a single bone is asymmetric with the most marked changes being found on the radial aspect (Fig. 2, *A* and *B*).

3. *Hyperparathyroidism*.[15] Pugh[10] stated, "Roentgenograms of the hands are of the greatest aid in the diagnosis of hyperparathyroidism." The subperiosteal resorption of the bone (the most dependable sign) is seen at the earliest time and most frequently along the margins of the middle phalanges of the fingers. It is a peculiar lace-like pattern of decalcification and almost pathognomonic of this condition. In an affected phalanx, 4 types of cortical changes may be seen: (a) generalized thinning of the cortex, (b) vertical linear bands of decalcification giving the cortex a lace-like appearance, (c) small deep central cortical erosions, and (d) small subperi-

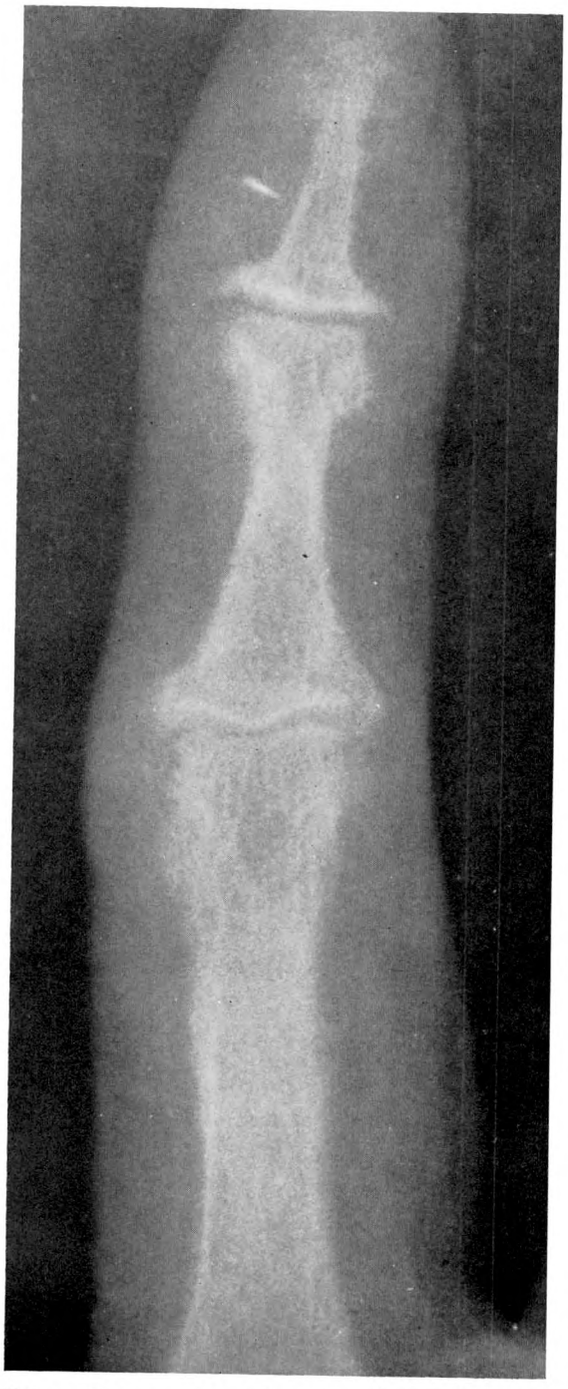


FIG. 3. *Hyperparathyroidism.* Irregular cortical contour with lace-like appearance is caused by subperiosteal bone resorption.

osteal erosions. In severe cases, the tuft of the terminal phalanges may disappear (Fig. 3).

B. SOFT TISSUE CHANGES

1. *Hemangiomatosis.*[11] Hemangiomas can be recognized by the presence of large tortuous vessels extending through the fatty tissue of the subcutaneous area. Large angiomas involving the skin appear as large irregular outgrowths of tissue. If veins participate, phleboliths will frequently be present. A racemose collection of tortuous dilated vessels, particularly in the subcutaneous tissue, is characteristic of hemangioma (Fig. 4).

2. *Lymphedema.*[11] Edema is recognized by an increase in thickness and density of the subcutaneous fat. The fibrous septa, due to their absorption of fluid, stand out prominently. The facial planes are obliterated (Fig. 5).

C. CHANGES IN THE TUFTS

1. *Scleroderma.*[8] Absorption of the tip of one or more terminal phalanges is a com-



FIG. 4. *Hemangioma.* Irregular soft tissue swelling. Large tortuous vessels can be discerned at the region of the head of the second metacarpal.



Fig. 5. *Lymphedema.* Only uniform soft tissue swelling is evident. There is a loss of distinction of fat and subcutaneous tissue.





Fig. 7. *Leprosy (neural type).* There is marked resorption of phalanges of all digits.

mon manifestation frequently before vascular disturbances are present. Associated calcifications of soft parts are comparatively common (Thibierge-Weissenbach syndrome) (Fig. 6).

2. *Leprosy.* In the lepromatous type, even in advanced cases, there is usually no gross destruction of bone unless there is

Fig. 6. *Scleroderma.* Bone resorption at the terminal tufts of digits 3 and 5, as well as soft tissue calcifications at distal phalanx 3 and distal interphalangeal joints, is noted.

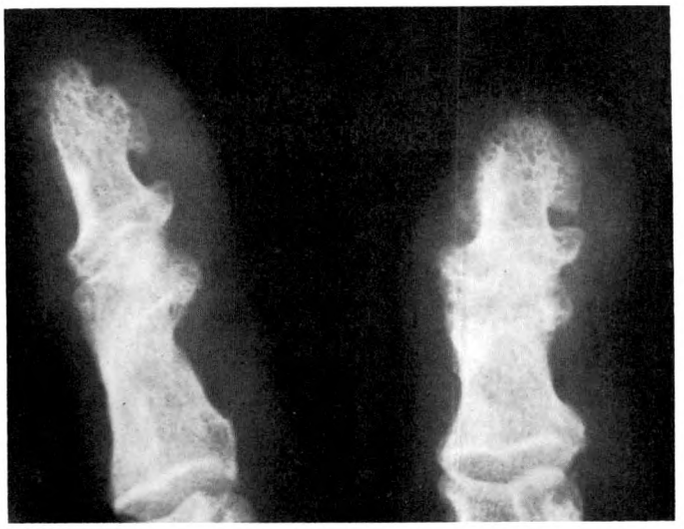


FIG. 8. *Acromegaly.* There is marked prominence of the terminal tufts, the "spade" configuration.

superimposed neural involvement. In neural leprosy the changes in the bone consist of slow and insensitive bone absorption. In the hands, the first abnormality is absorption of the tuft. Several fingers and toes are usually affected. Gradually, the distal aspects of the phalanges become absorbed. In most cases the absorption of the bone is arrested when the metacarpophalangeal joints have been reached (Fig. 7).

3. *Acromegaly.*[6] The so-called "spade hand" of acromegaly is predominantly the result of soft tissue hypertrophy. The joint spaces are abnormally wide due to hypertrophy of the cartilage. There may be squaring and thickening of the phalanges or narrowing of the shafts of the same bones. The ridges of the bones of the hands are prominent. The enlargement of the tufts of the terminal phalanges is a salient feature, particularly in males (Fig. 8).

D. CHANGES IN THE WRISTS

1. *Lead intoxication.* The most common heavy metal poisoning is chronic lead ingestion. The so-called lead lines are usually more prominent in the region of the rapidly growing bone areas, such as the wrists, knees, and ankles. Roentgenograms of the hands will include dense lines on the distal aspects of the radius and ulna (Fig. 9).

2. *Rickets.* Roentgenographically, the most marked changes are noted in those areas of bone which grow the most rapidly. Those regions also show the earliest changes. The bones are demineralized and have a coarse texture. The metaphyseal end of the long bones is irregular and presents a "brick-like" appearance. The bone is soft and, because of muscle pull and weight bearing, the ends may be cup-shaped (Fig. 10).



FIG. 9. *Lead intoxication.* There are dense zones at the metaphyses of the radius and ulna.

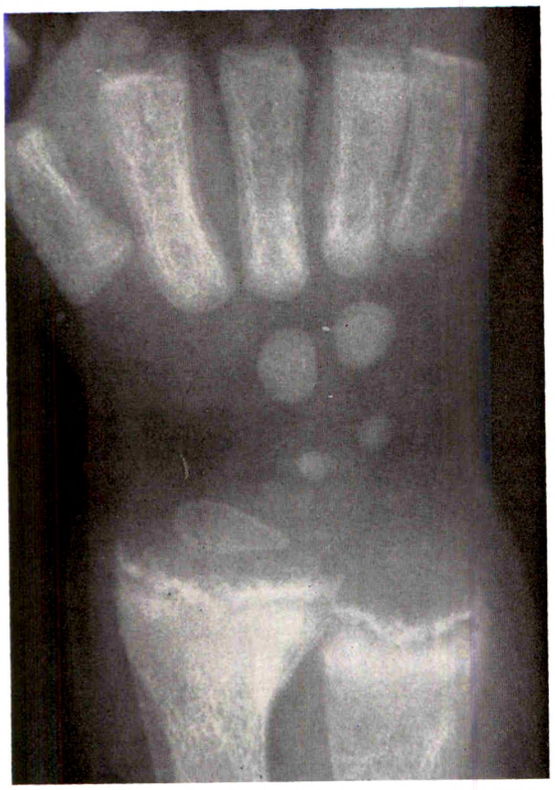


FIG. 10. *Rickets.* There are irregular, cupped metaphyses and widening of the zone of provisional ossification of the radius. Similar metaphyseal changes at the metacarpals are seen, as well as bone demineralization.

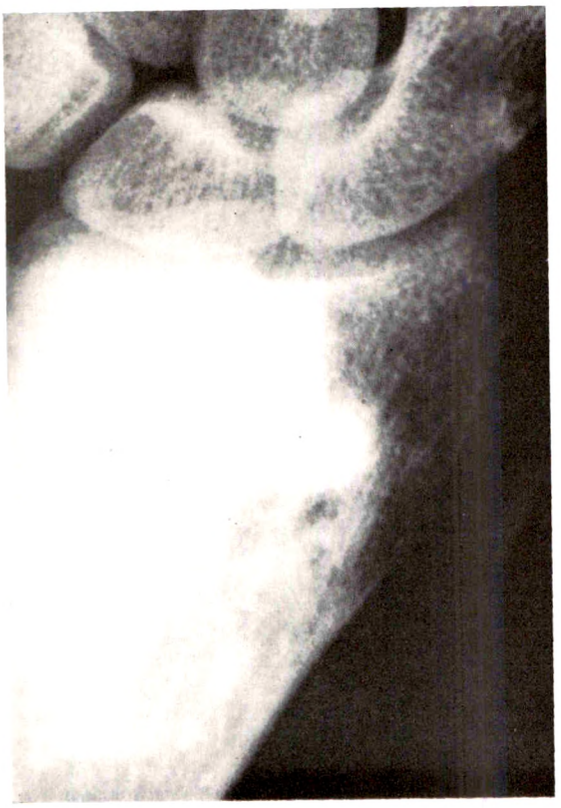




FIG. 12. *Metastasis from carcinoma of the lung.* There is destruction of the major portion of the distal phalanx, associated with soft tissue tumefaction.

3. *Brown cysts of hyperparathyroidism.* In this condition, small or large cyst-like lesions are seen quite frequently. They may expand the bone and give the appearance of giant cell tumors. Cyst-like lesions in the cortex of the bone are most suggestive of hyperparathyroidism. These lesions heal after the primary condition is treated. This

FIG. 11. *Hyperparathyroidism.* A parathyroid adenoma was removed several years ago. A "brown tumor" seen at the distal radius presents as dense calcification.



FIG. 13. *Gout.* Tophi seen as soft tissue masses cause bone erosion at second metacarpophalangeal joint, third proximal interphalangeal joint and distal fifth metacarpal.

does not occur always, and the lesion can present as dense calcification[2] (Fig. 11).

E. DESTRUCTIVE AND LYTIC CHANGES

1. *Metastasis.*[4,9] In spite of its rarity, peripheral metastasis should be included in the differential diagnosis of lytic lesions of the bones of hands and feet. The lesions frequently occur in the phalanges, particularly on the distal ones. This may be related to the brisk arterial flow to the ends of the digits. Mulvey[9] stated that no record of carpal bone metastasis has been found. The lesions closely simulate osteomyelitis; they are purely osteolytic without reactive bone formation. The adjacent trabeculae are normal in appearance. In Mulvey's reported cases and in about one-half of the reported cases in the literature, the primary malignant neoplasm has been found in the lung (Fig. 12).

2. *Gout.* Narrowing of the joint space with a sharply defined, punched-out erosion of the articular cortex is typical of gout. The surrounding bone is not dense but of normal trabeculation. The small interphalangeal joints are frequently affected. The punched-out lesions can be seen also in the carpal bones (Fig. 13).

3. *Enchondromatosis.*[13] The chondromatous lesions may appear as irregular, ill defined defects, or sharp "punched-out" radiolucent areas. The bone may be expanded and small calcifications may be present within the lesions (Fig. 14).

4. *Sarcoidosis.*[5] Lesions of sarcoidosis are frequently seen in the shaft of the phalanges or heads of the metacarpals. The middle and distal phalanges are usually affected. The most frequent manifestation in the roentgenogram is a pattern due to



FIG. 14. *Enchondromatosis.* There are multiple radiolucent lesions in the phalanges, well circumscribed, and expanding the cortex. Amorphous calcifications in the lesions at the distal aspect of the proximal phalanges of the thumb and middle finger are present.



Fig. 16. *Thalassemia.* A coarse trabecular pattern, thin cortex and lack of tubulations of bone are demonstrated.

absorption of the small reticular trabeculae. Cystic lesions, small or large, measuring usually 3 to 5 mm. in diameter, with the longer diameter in the direction of the long axis of bone with a narrow sclerotic rim, are noted in the more advanced cases (Fig. 15).

F. DIFFUSE CHANGES

1. *Thalassemia.* The bone changes in thalassemia are generalized to all bones.



Fig. 15. *Sarcoidosis.* Subcortical and periarticular cystic dissolutions and bone resorption at the terminal tuft of the index finger are present.



Fig. 17. *Pituitary dwarfism.* Patient, aged 39 years. Lack of fusion of epiphyses.



FIG. 18. *Rheumatoid arthritis*, far advanced, in a child. There is narrowing of the joint spaces, ulnar deviation of digits 4 and 5, bone atrophy, and irregularity of the carpal bones with several cystic dissolutions.

There is a diffuse coarse trabecular pattern due to loss of some but not all of the trabeculae and prominence of the remaining ones. The cortex is thin. The shape of the metacarpals is rectangular due to expansion of the middle part of the shaft (Fig. 16).

2. *Pituitary dwarfism.* Roentgenograms of the hands are very useful for the evaluation of bone maturation. In pituitary dwarfism there is retardation of epiphyseal maturation with bones otherwise normal or slightly abnormal in shape (Fig. 17).

3. *Rheumatoid arthritis.*[3,7] In this condition, there is narrowing of the joint spaces, particularly of the proximal interphalangeal, the intercarpophalangeal and the wrist joint spaces. The wrist shows early changes of the ulna with soft tissue swelling and typical erosion of the cortex on the medial aspect of the ulnar styloid. Characteristically, para-articular soft tissue swelling, as well as surface or marginal erosions and trabecular loss of bone, are also present. The routine roentgenograms of hands, wrists, and feet are an important aid in the early diagnosis of rheumatoid arthritis (Fig. 18).

4. *Nerve injury.* When there is loss of efferent nerve function, there is loss of volitional nerve-muscle control. The affected extremity will show generalized atrophy of the soft tissues (muscles), widespread de-ossification, thinning of the articular cortices and normal joint spaces. There is multiplicity of involvement (Fig. 19).



FIG. 19. *Nerve injury.* There is periarticular bone demineralization and demineralization of the carpal bones. Opaque sutures at the wrist are noted.

SUMMARY

Some of the more common and several uncommon generalized diseases which can be detected in roentgenograms of the hands are discussed in an approach utilizing analysis of roentgen features.

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TRABECULAR PATTERNS IN BONE*

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SKELETAL roentgenograms represent a single plane descriptive gross image of the complex three dimensional cortical and cancellous structure of bone. The roentgen image does not record the exact anatomic trabecular and cortical detail of bone, but rather depicts photographic patterns that are produced by overlay, groupings, and accumulations of large numbers of fine and coarse trabeculae. By correlation with clinical experiences and normal physiologic variations, certain characteristic roentgen images have been recognized and identified with specific diseases and abnormalities.

There has been much investigation regarding the significance and techniques of measurement of bone density and the responses of supporting trabeculae to external demands.[10,12,14,16,19,20,31,36,41] However, relatively little attention has been paid to the internal architectural design of bone trabeculae and the characteristic patterns associated with clinico-pathologic alterations. It is common to note that the number and strength of the longitudinal trabeculae increase on the weight bearing side and absorb on the non-weight bearing side of wedged vertebral bodies[34] and angulated bones.[41] Moderate sustained pressure applied to bone produces osteogenesis, and excessive pressures result in osteolysis. The physiologic reasons for these responses have not been explained. In view of the great variation in the normal internal architectural structure of bone, an understanding of its appearance in weight bearing and non-weight bearing areas in childhood, adolescence, adult life and in the aged, as well as its response to trauma, disuse, vascular alterations and disease, is essential. This introductory report of a more extensive evaluation of trabecular patterns in bone and alterations that occur in health and disease outlines preliminary clinical and experimental observations regarding bone atrophy, avascular necrosis and graft incorporation.

Basically, bone consists of relatively broad trajectory trabeculae which are concerned with support and weight bearing along major lines of force and stress.[19,20,28,30,35,41] The intervening fine mesh trabeculae add further strength to the main trabeculae and permit absorption of complex stresses in terms of changing dynamic pressures applied through mobile joint surfaces. In areas where major directional stresses can be well defined, such as at the calcar femorale, major trajectory trabeculae can be observed. Where stresses of weight bearing and muscle pull are constantly subjected to changing forces, such as at joint surfaces and bone ends, ilium and ribs, fine trabeculae predominate. Since both the coarse trajectory and the fine cross bracing trabeculae are concerned with the same basic supporting function, dynamic alterations represent responses to mechanical demands and metabolic variations in health and disease.

BONE ATROPHY

Wolff's original concept that lack of function is coupled with bone absorption has been borne out by clinical observations. Post-traumatic bone absorption was described by Volkmann and amplified by the observations of Sudek.[18] Similar atrophy of bones, as well as their supporting ligaments, has been noted in proximity to infection and inflammation, and as the result of immobilization and disuse.[8,13,21] Greig[15] and others postulated that the hyperemia resulting from immobilization and disuse caused rarefaction by loss of both matrix and mineral. This relationship between hy-

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peremia and bone absorption was stressed by Watson-Jones and Roberts,[39] Bobechko and Harris,[6] and Geiser and Trueta.[13]

In the diagnosis of bone atrophy on the roentgenogram, it is most common to refer to the decreased density of a particular bone or portion of bone. Various methods have been devised to measure the density of bone[4,9,11,18,23,27,38] but variations in technique, lack of homogeneity of bone as a structure, and other difficulties have made these measurements of limited clinical value. Babaiantz[3] showed that only after about 30 per cent decalcification of bone can demineralization be suspected on the roentgenogram, and a loss of 50 per cent is necessary for the findings to be unequivocal. Experimental removal of an entire quadrant of the femoral head in the anterior or posterior portion is not detectable on the roentgenogram in certain positions.[5] Since such a large amount of bone may be absent before it is grossly visible on the roentgenogram, reliance upon either a visual interpretation of the roentgenogram, or upon methods of density measurement may be misleading.

Allison and Brooks[1] noted that as a result of disuse the earliest changes in bone occurred in the cancellous portion and consisted of absorption of bone trabeculae. In order to obtain a more accurate impression as to the dynamic changes that are occurring, it is essential, therefore, to study the individual trabecular pattern of the involved bone compared with the normal side, with the normal pattern for that bone at that specific age, or with roentgenograms of the bone itself prior to the onset of the process of atrophy.

Different trabecular patterns may be observed in bone atrophy of disuse[33] with variations in this pattern of different age groups and in bone of different location. For example, the first areas to exhibit bone absorption are in the region of the closed growth plate at the end of a long bone in the adult, and the subchondral area adjacent to a joint surface.

Early bone atrophy is manifested by a change in appearance, both of the fine cross bracing and the main weight bearing trajectory trabeculae. Changes in the fine trabeculae are often visible before gross alterations in bone density are apparent. Basically, these may be (1) thinning of individual trabeculae, (2) interruption of continuity of individual trabeculae, or (3) focal absorption of most trabeculae in a single area producing spotty lytic appearances. The appearance of the broader main trajectory trabeculae is also altered as bone atrophy progresses. The fine trabeculae are much like a veil, overlying and modifying the pattern of the primary trajectory trabeculae. As the fine trabeculae absorb in the earliest phase of bone atrophy, the remaining heavier trabeculae stand out more prominently against the contrasting background.

Experimentally, this appearance can be reproduced by simple *in vitro* decalcification of slices of the weight bearing portions of long bones (Fig. 1, *A* and *B*). One-half inch thick frontal sections of the lower femur and the upper femur were suspended in a solution of 5 per cent nitric acid and removed at one-half hour periods for roentgenographic examination until full decalcification.

As *in vitro* halisteresis occurred by the solution of calcium salts on all of the trabecular surfaces, the smaller fine trabeculae were the first to demonstrate alterations. The grossly frosted appearance produced by the overlying and surrounding mass of cancellous fine trabeculae in normal bone, such as the femoral head or the distal femoral condyle, partially obscures the main supporting trajectory trabeculae. Increasing degrees of decalcification produced roentgen patterns of fine trabecular thinning, discontinuity, and absorption. Further decalcification diminished the over-all background veil of fine trabeculae and permitted the main supporting trajectory trabeculae to stand out in contrast.

In early bone atrophy, large and small trabecular surfaces are probably subjected to the prevailing osteolytic influences

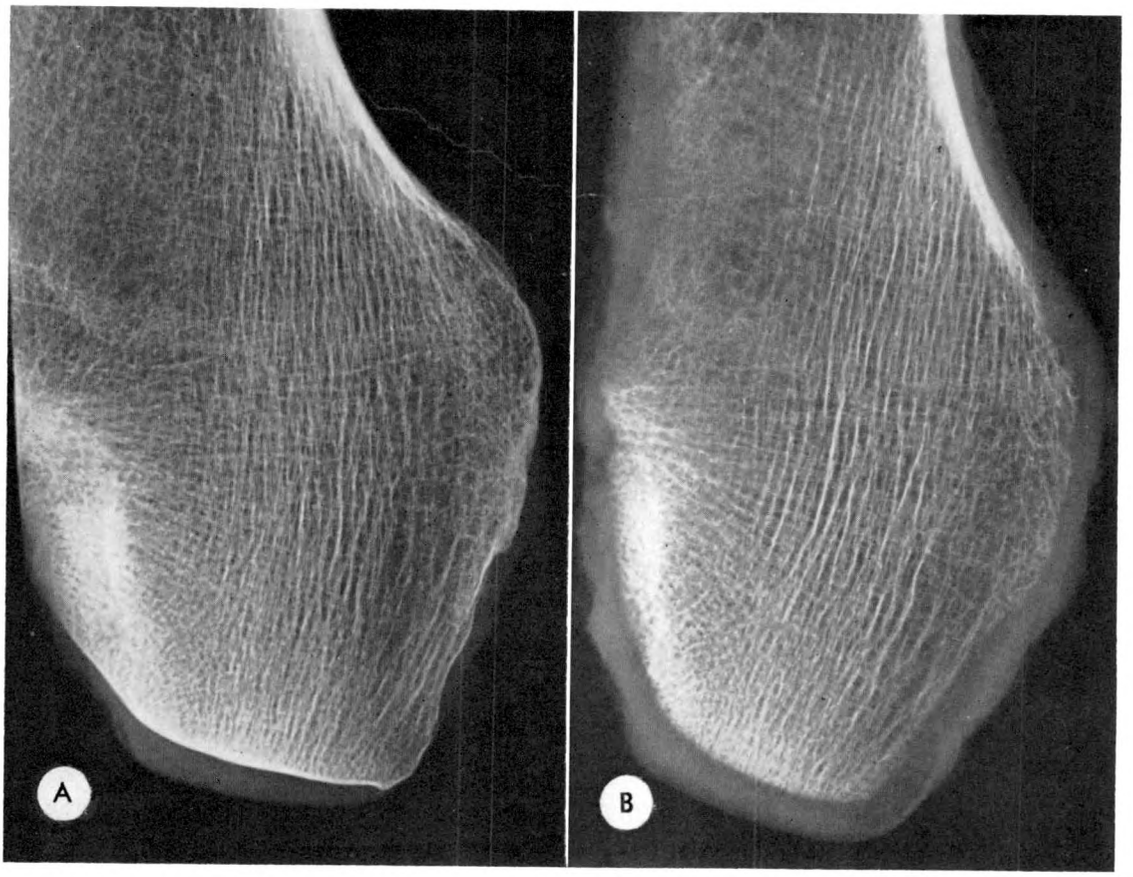


Fig. 1. Anteroposterior roentgenograms of a one-half inch thick frontal section of a distal femur from a 65 year old male. (*A*) Before decalcification. (*B*) After 3 hours partial decalcification in 5 per cent nitric acid. The veil of fine trabeculae has been partially removed by *in vitro* decalcification, leaving the appearance of thickening of the major longitudinal trajectory trabeculae.

simultaneously, although selected areas may be affected differently because of vascular supply. It is postulated that the fine mesh and cross-bracing trabeculae are the first to disappear on the roentgenogram, solely because of their relatively small size compared with the broader and thicker main weight bearing trajectory trabeculae. The result is the evolution of patterns of fine trabecular thinning, discontinuity, and eventual absorption, associated with apparent prominence of the main supporting trabeculae which simulate patterns produced by *in vitro* decalcification.

Experimentally, bone atrophy of the os calcis of 10 chinchilla rabbits was produced by closed fracture of the tibia. Disappearance of the fine trabeculae and apparent coarsening of the main trajectory trabeculae were observed. The roentgenographic appearance was similar to that noted in the experiments of Geiser and Trueta,[13] where atrophy was produced by muscle section and immobilization. When more longstanding disuse was produced by repeated refracture of the tibia over a 3 month period in 15 rabbits, the major trabeculae themselves began to absorb.

When the process of atrophy ceases, and the stage of repair begins, endosteal osteogenesis can be noted histologically. In an attempt to study the healing phase following a stage of atrophy, 6 adult mongrel dogs were employed. The midshaft of the femur was transected with a motor saw by open

operation, and internal fixation was performed by use of a four-hole plate. The animals favored the extremity for a few weeks and then used it normally. They were sacrificed at the end of 6 months, and the os calcis was studied by roentgenographic and histologic techniques. During the phase of atrophy, the fine trabeculae had absorbed, but, during the stage of repair, the original fine trabecular pattern was not completely re-established. Instead, the main trajectory trabeculae thickened, producing a coarsened final pattern (Fig. 2, *A* and *B*). The mechanism for the formation of this altered pattern, following a phase of bone atrophy, appears to be based on the principles of economy of bone structure. During the process of severe atrophy, which is a surface osteoclastic absorption phenomenon, many of the fine trabeculae disappear completely and the coarse trabeculae may be thinned. Once the process of repair begins, osteogenesis, arising from proliferation of endosteal elements, results in the formation of new bone on existing trabecular surfaces.

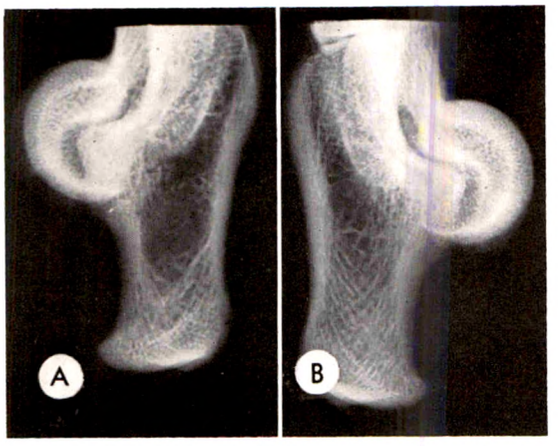


Fig. 2. Lateral roentgenograms of the os calcis of a dog in which open fracture of the femur with internal fixation was performed on one side. (*A*) The animal guarded the extremity for several weeks and then walked normally. At the end of 6 months, the roentgenogram reveals that the fine mesh trabeculae had absorbed and not reformed. There is thickening of the main trabeculae of the os calcis. (*B*) Unoperated side showing the normal fine mesh trabecular structure.

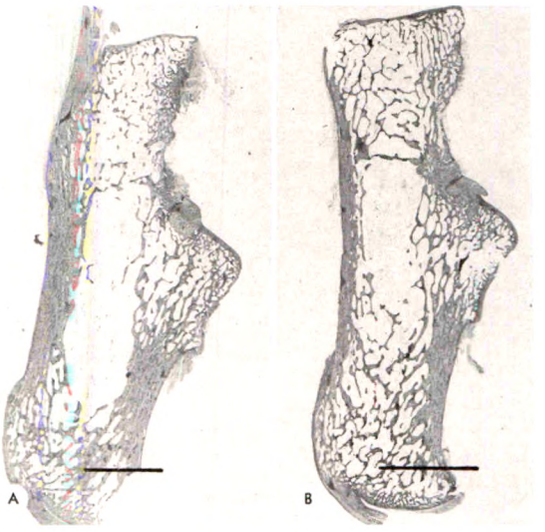


Fig. 3. Photomicrographs of a hematoxylin-eosin stained section of the os calcis shown in Figure 2, *A* and *B* (×4). (*A*) On the operated side, most of the fine trabeculae in the posterior os calcis have absorbed with concomitant thickening of the remaining major trabeculae. (*B*) Unoperated side.

The major scaffold for the invading new bone is represented by the unabsorbed heavier primary supporting trabeculae. Thickening of these trabeculae then appears to occur until such mechanical point that the over-all strength of the bone is restored (Fig. 3, *A* and *B*). This new design is sufficient to maintain skeletal integrity without the need to re-establish the finer cross-bracing structure. Therefore, once the normal trabecular pattern has been seriously affected as a result of bone atrophy, many of the fine trabeculae have been absorbed and are no longer available as a scaffold or template for new bone formation. A less compact and new pattern of intertrabecular bracing trabeculae forms to supplement the stronger thickened trajectory trabeculae. In a weight bearing bone, it is common to note permanent residual coarsened trabecular patterns following a phase of bone atrophy such as immobilization and fracture (Fig. 4).

Reconstitution of the normal original fine trabecular architecture of bone is most commonly observed following atrophy in youthful, non-weight bearing bones, and in



Fig. 4. Roentgenogram of the knee of a 16 year old female with ulcerative colitis and rheumatoid-like arthritis, who has had joint contractures and had been on steroid therapy for several years. The main longitudinal trabeculae have thickened and the fine cross-bracing trabeculae have absorbed as a result of bone atrophy.

bones bordering on joints where there is normally a high concentration of fine trabeculae and paucity of major trajectory trabeculae (wrist, head of humerus). In these areas there are constantly changing mechanical forces in contrast with the static forces present in weight bearing bones.

AVASCULAR NECROSIS

The early diagnosis of avascular necrosis is generally based upon a relative increase in density of the involved area on the roentgenograms compared with the adjacent bone. Many investigators[6,22,25,40] have postulated that the increased density of the femoral head in avascular necrosis following intracapsular fracture represents only a relative hyperemic atrophy of adjacent bone. Actual increased density of the necrotic fragment has been suggested by Phemister[24] as a result of calcification of dead bone, and by Bobechko and Harris[6] to be due to invasion of new bone advancing along the necrotic trabeculae. The validity of findings of experiments employing radioactive materials,[2,7,37] blood flow measurements,[17,29] and biopsy as early signs of aseptic necrosis will depend upon long-term clinical correlations. In orthopedic practice, since rather large amounts of bone must be removed before changes in bone density are visible on the roentgenogram, the clinical diagnosis of avascular necrosis generally must await the appearance of relatively late deformity of the head.

In his discussion of avascular necrosis, Phemister[24] confirmed the observation that necrotic bone retains its original architecture because of its failure to take part in the surrounding bone atrophy. Watson-Jones[40] presented a histologic specimen of a 6 week old fractured patella, demonstrating absorption of trabeculae in the living segment but persistence of normal thickness and density of trabeculae in the necrotic portion.

In an attempt to gain a better understanding of the early changes in aseptic necrosis, the observations relating to trabecular alterations in bone atrophy have been used as the basis for study of internally fixed fractures of the femoral neck for the last 15 years. Since the fine trabecular structure is the first altered by hyperemia and atrophy in viable bone, often before gross changes in bone density are apparent, the trabecular pattern of femoral heads in intracapsular fractures has been studied. It has often been possible to predict avascular necrosis at a relatively early stage after internal fixation of an intracapsular fracture of the hip. Atrophy and absorption of bone within the neck and intertrochanteric area of the femur, where cross-bracing and transverse transom trabeculae are normally relatively sparse, may be recognizable within a relatively short time after injury

(3–4 weeks). Although occasionally visible this early, the more closely packed and denser trabeculae of a viable head may not begin to demonstrate absorptive changes until slightly later (5–12 weeks). It is essential to obtain a roentgenogram of the pelvis, including both hips in internal rotation, soon after surgery, noting positioning of the patient and the exposure employed for future reference. Initial roentgenograms and operative controls are often not sufficiently detailed technically. If displaced, the femoral head may be in a different position than that following reduction and fixation, making later comparisons difficult. As a result of relative disuse, it is common for some atrophy to occur in the head, neck, and intertrochanteric area on the normal side, but generally to a lesser degree than on the injured side. Since there are frequent variations in the trabecular pattern as a result of bone atrophy, probably due to normal variations in the internal architecture of bone and vascular supply, it is particularly important to compare the normal with the injured side.

If absorption of the fine trabecular structure can be identified on the injured side in comparison with the original postoperative roentgenograms in 6 to 12 weeks, a positive diagnosis of a viable head can be made (Fig. 5, 6 and 7). In instances of nonunion or delayed union of intracapsular fractures, the type of reconstructive procedure to be performed (*i.e.*, prosthesis or osteotomy) may depend upon whether or not the femoral head is alive (Fig. 8 and 9).

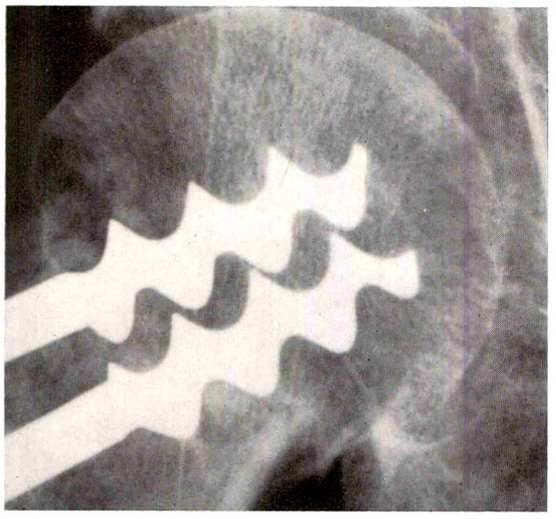


Fig. 5. Roentgenogram of the hip in a 60 year old female 8 weeks after fixation of an intracapsular fracture with two Lippmann bolts. Signs of bone atrophy, manifested by trabecular absorption and discontinuity, are visible in the outer segment of the femoral head and indicate maintenance of vascularity and viability.

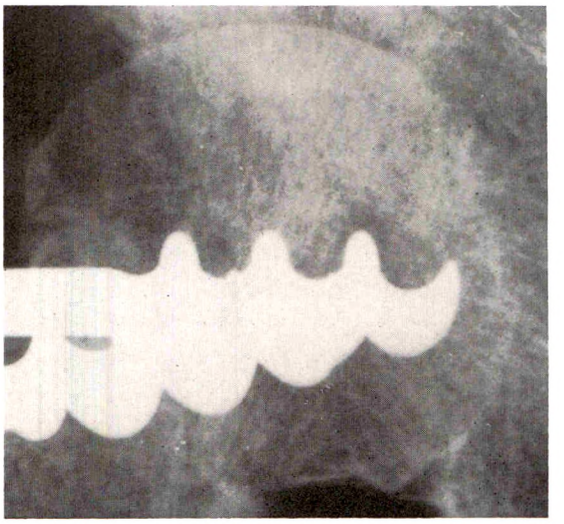


Fig. 6. Roentgenogram of the hip in a 52 year old female 12 weeks after fixation of an intracapsular fracture with two Lippmann bolts. Signs of bone atrophy are evident by alterations in the trabecular structure of the outer and inner portions of the femoral head.

There is a significant variation in time as to when the signs of bone atrophy appear. Therefore, no attempt has been made to employ the persistence of the fine trabecular pattern in the head as a sign of avascular necrosis. Since vascularity of the femoral head is generally unimpaired in fractures below the femoral neck, the alterations in trabecular patterns within a viable femoral head can be studied by observation of cases of intertrochanteric or upper femoral fractures. The earliest signs of trabecular absorption in the femoral head are often in the non-weight bearing area at the upper-outer or lower-inner poles which are not obscured by the overlapping acetabular shadow. Abduction and adduction views

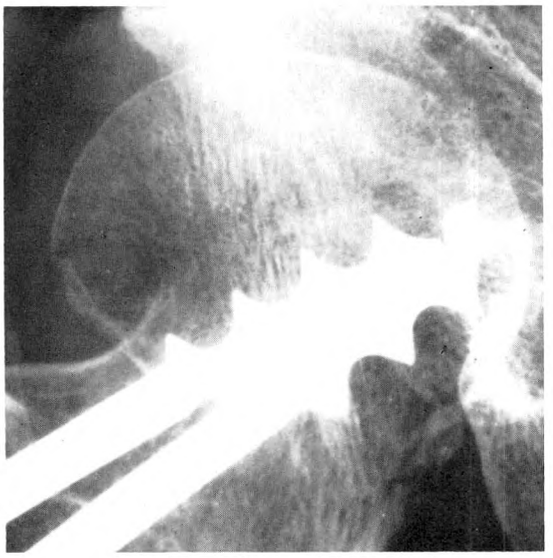


Fig. 7. Roentgenogram of the hip in a 56 year old female seven weeks after fixation of an intracapsular fracture with two Lippmann bolts. There is almost complete absorption of fine trabeculae in the outer portion of the viable femoral head. Two weeks previously the roentgenogram showed the same normal fine trabecular structure seen in the immediate postoperative roentgenograms.

may be helpful for better visualization of these areas.

Necrotic free bone fragments in comminuted fractures can be differentiated from those where soft tissue attachments maintain viability. In the latter, fine trabeculae within the cancellous section are absorbed rapidly and relative coarsening of the pattern may be observed within a few weeks. In avascular necrosis of the talus, the anterior section of the neck and the subchondral bone are generally the first areas to demonstrate alteration in trabecular patterns.

BONE TRANSPLANTS

Phemister[26] demonstrated that bone grafts presented a dense appearance on the roentgenogram compared with that of the osteoporosis of surrounding bone. He concluded that this was evidence of avascular necrosis of the transplants. This observation has been confirmed by subsequent clinical and experimental findings. Some surface cells undoubtedly survive transplantation, but it is probable that they play a relatively minor role in the over-all clinical success or failure of the bone graft procedure.[32] Success of incorporation of a graft depends primarily upon the host's potential for new bone formation. Although a well tolerated autogenous graft appears to stimulate osteogenesis, for the most part the graft itself is largely a scaffold on which invading new bone may grow.

Density determinations of transplants are impractical because of many variable elements, including graft size, overlap, and positioning. By application of the principles of bone atrophy to the roentgen appearance of a transplant, it has frequently been possible to determine its probable fate at an early stage; namely, whether a cancellous graft is absorbing, is dormant, or is in the process of incorporation. A transplant introduced into a bone defect or applied to the surface of bone to assist in healing is surrounded by hematoma, which is soon replaced by granulation tissue and multipotential mesenchymal tissue. In a favorable environment, new bone arises from host osteogenic sources, invades the graft,

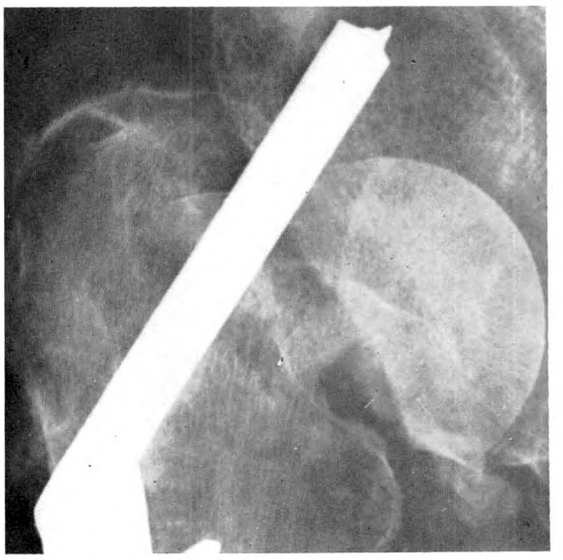


Fig. 8. Roentgenogram of an unhealed displaced intracapsular fracture in a 66 year old male 6 months following injury. Persistence of the original fine mesh trabecular pattern in the femoral head indicates avascular necrosis.

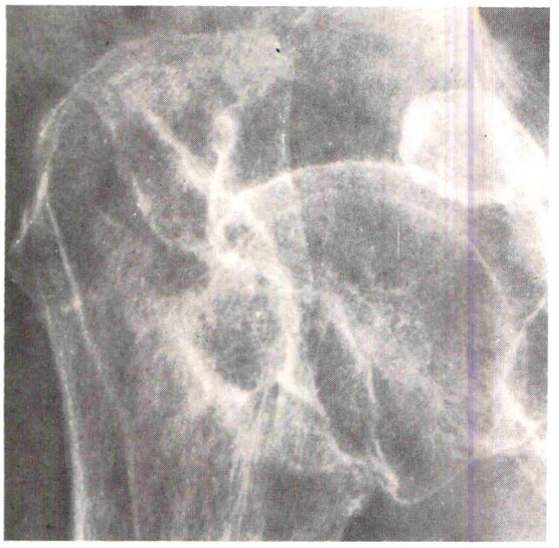


Fig. 9. Roentgenogram of an unhealed intracapsular fracture in an 82 year old female 2 years postoperatively, after removal of a Smith-Petersen nail. Bone atrophy and trabecular absorption are signs of a viable head.

and advances along the necrotic transplant trabeculae. Endosteal elements of the transplant that survive also proliferate to fill the intertrabecular spaces. The earliest signs of graft incorporation, therefore, are thickening of the existing trabeculae and haziness of the trabecular outline because of osteogenesis within intertrabecular spaces (Fig. 10).

In an unfavorable bed, such as occurs when there is poor vascularity, poor host osteogenic potential or fibroplastic influences such as motion, the graft remains dormant in its bed. As it is being absorbed,



Fig. 10. Roentgenogram of an autogenous iliac transplant applied to the nonunion site of an ulna in a 24 year old female 3 months postoperatively. Thickening of the trabeculae within the transplant indicates invasion by new bone and early incorporation.

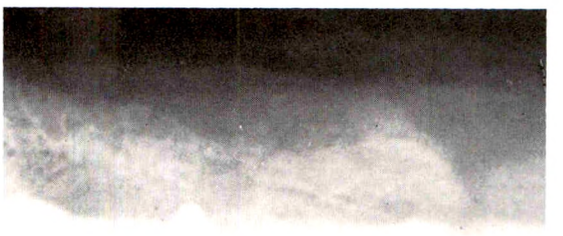


Fig. 11. Roentgenogram of an autogenous iliac transplant applied to a nonunion site in the tibia of a 58 year old female 9 weeks postoperatively. Trabecular discontinuity and absorption indicate transplant atrophy as a result of vascular invasion without new bone formation.

osteolysis and granulation tissue invasion of the transplant are manifested by the signs of atrophy; namely, thinning, discontinuity and eventual destruction of the fine trabecular structure (Fig. 11 and 12).

Occasionally, a slightly delayed but vigorous osteogenic front arising from the host bone may contact and invade a graft that has undergone some degree of atrophy and demonstrates roentgen signs of early absorption. The remaining unabsorbed trabeculae may then serve as a scaffold for the invading new bone. Generally, on serial roentgenograms, careful study of both the degree of new bone formation occurring at a fracture site or bone defect

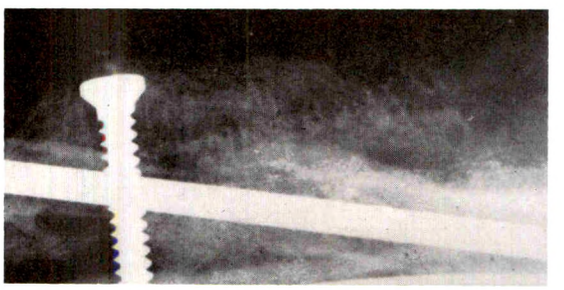


Fig. 12. Roentgenogram of an autogenous iliac transplant employed for nonunion of a fracture of the radius and ulna in a 34 year old female, 4 months postoperatively. Absence of broadening of the trabeculae and increased density of the intertrabecular spaces are evidences of failure of osteogenesis within the transplant. Signs of atrophy, with trabecular absorption and discontinuity, indicate early transplant absorption.

and the internal architectural trabecular changes occurring within the graft gives an accurate indication as to the stage and degree of reparative osteogenesis and graft incorporation.

Loss of continuity and thinning of the trabeculae, or areas of focal absorption of the transplant, are the earliest signs of failure of incorporation of a cancellous graft. Frequently, the larger and medium sized trabeculae remain after disappearance of the fine trabeculae, giving the appearance of coarsening.

CONCLUSIONS

Study of the changing trabecular patterns of bone on serial detailed skeletal roentgenograms of good technical quality frequently affords the orthopaedic surgeon an opportunity to detect early signs of bone atrophy, avascular necrosis and bone transplant incorporation.

In general, characteristic patterns of atrophy can be recognized in each bone, depending upon its normal concentration of fine and coarse trabeculae. The fine trabeculae are the first to demonstrate alterations consisting of thinning, discontinuity and absorption during the early stages of bone atrophy. Maintenance of the fine trabecular pattern in the presence of atrophy of surrounding bone is often an indication of avascular necrosis, particularly in the head of the femur following intracapsular fractures and in the talus following extensive bone resection required in foot stabilization.

Following a phase of bone atrophy and absorption of the fine trabeculae, it appears that reconstitution of bone strength occurs by thickening of the remaining primary trabeculae which serve as a scaffold for invading new bone. Reformation of the original fine trabecular structure is uncommon, and the coarsened trabecular pattern is a permanent documentary evidence to the past history of the bone.

Discontinuity of trabeculae in the light of poor host osteogenic response is frequently the earliest sign of transplant absorption and failure of incorporation. Increased density of the graft as a result of osteogenic thickening of the trabeculae, or invasion of intertrabecular spaces by new bone, generally indicates early bone transplant incorporation.

Prompt recognition of the significance of these early signs of bone necrosis and bone absorption is of value to the orthopaedic surgeon in evaluating the timing and appropriate selection of reconstructive operative procedures.

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AUTOMATION OF FILM VIEWING—A NEW DEVICE—THE PANORAMASCOPE*

By PAUL C. HODGES *and* CLYDE M. WILLIAMS
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AS LONG as the studying and filing of radiographs remained a small-scale operation it was practical to rely on individual resourcefulness, systematic organization being unnecessary. There is nothing small-scale, however, about film handling in large, modern teaching hospitals and organization must be well conceived and executed if chaos is to be avoided. In the United States the problem had to be faced for the first time in World War I military hospitals when radiographs were glass plates rather than films. Large viewing rooms were equipped with numerous double-deck sloping front view boxes and throughout the day the developed, fixed, washed but still wet X-ray plates stood on such boxes, glass side out, so that viewing and drying were carried on simultaneously. The almost universal American practice of putting numbers on films "backward" is vestigial from such viewing of glass plates where it had the advantage of allowing one to read the numbers correctly through the glass side rather than the wet emulsion side of the plate. With the advent of films, the old system gradually was abandoned (except for reversed numbers), dried films being kept in large envelopes (usually referred to as jackets) to be put on view boxes as needed.

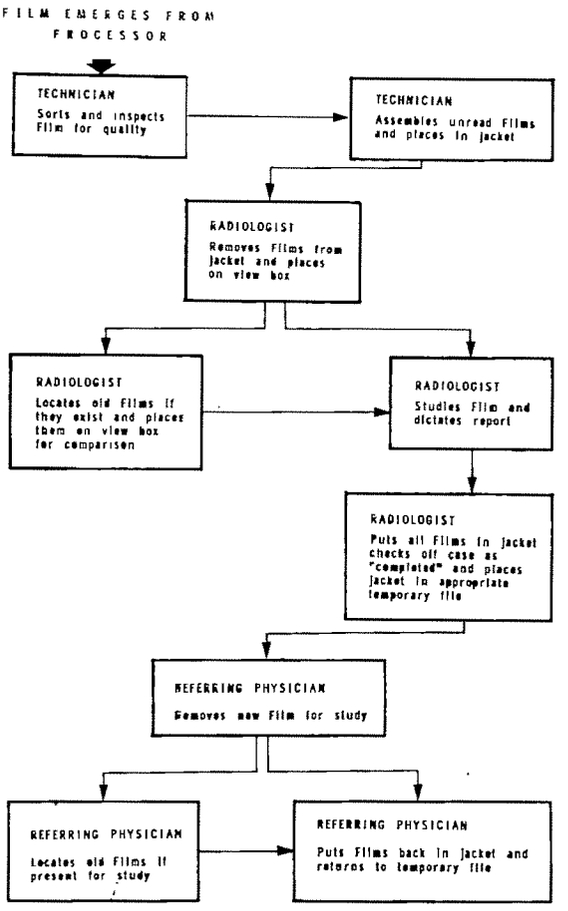


FIG. 1. Film flow in the absence of mass viewers (University of Florida).

Many European and some American teaching hospitals have mechanized the daily viewing of X-ray films but in many more, like our own, radiologists and other physicians have been handling from 5,000 to 10,000 individual films each week laboriously taking them out of their jackets, sorting them, looking at them, putting them back in jackets (hopefully the proper films in the proper jackets) following which numerous other physicians have done the same things to the same films throughout the remainder of the day. Time studies at our institution show that the average time expended on each film has been 0.34 minutes so that with an average of over 5,000 films a week we have been wasting annually on film handling almost the full time of one radiologist to say nothing of similar expenditures of time by physicians on other services (Fig. 1).

* From the Department of Radiology, University of Florida College of Medicine, Gainesville, Florida.

SINGLE BELT VIEWER

Recently we have constructed a mass film viewer, the Panoramascope, and when we have been able to provide it in quantity, are confident it will save much time for all who view our films. The heart of the instrument is a two layer belt of sheet Mylar 0.003 inch thick, 17 1/4 inches wide and 250 feet long, which is driven by motorized spools across the face of a 17 inch × 60 inch view box. We refer to the belt as a "belt-envelope" because its two layers of Mylar are continous below, open above, and closed vertically at 60 inch intervals by means of heat sealing tape to form 50 numbered envelopes or pockets, each capable of holding four 14 inch×17 inch films. By means of normal-speed and high-speed switches, this belt and its 200 or more films may be moved rapidly in either direction at speeds of 4 or more feet per second (the entire 50 pocket belt in 50 seconds) or slowed down to 2 feet or less per second as the examiner approaches the pocket in which he is interested. Automatic switches prevent running the end of the belt off its spool.

The Panoramascope is made in two types, both of them double decked and both of such weight and dimensions that they can be moved on their rubber casters through standard doors and corridors from one room to another. The most generally useful type has a single-belt viewer below and a standard 17 inch×60 inch view box above (Fig. 2 and 3) but for certain special purposes, including conferences, there is a second type (not illustrated) in which both decks are belt-viewers. In both types the space below the lower deck is occupied by pigeon holes for the temporary filing of the packets of films displayed in the belts. Two pilot models of the single-belt type have been constructed in the experimental shops of the University of Florida and at the time of submitting this manuscript for publication we were anticipating early delivery of commercial models of both types.*

* Manufactured for us by RADX Corporation, P.O. Box 19164, Houston, Texas 77024.

FILM HANDLING WITH AID OF MASS VIEWERS

As films come from rapid processors clerks gather them, case by case, on the officer of the day's view box (we prefer the Philips Alternator), holding them there until he has checked all films including necessary repeats and has instructed the technician to release the patient. The films now are taken from the Alternator and placed in the pockets of the Panoramascope regularly assigned to the service from which the patient was referred. The technician's notes together with fluoroscopic or other notes made by radiologists during the course of the examination plus all of the papers and films from earlier examinations are placed in the jacket which is filed in the pigeon holes beneath the belt-viewer. Printed tally sheets with numbered boxes for each of the pockets are mounted on either side of the viewer and in these boxes clerks enter the patient's name and number, the fact that the officer of the day has reported the films (if such is the case) or the name of the radiologist assigned to report them and eventually the fact that he has done so. Such reporting is done without removing the films from the belts. As typed reports come from the stenographic pool, they are placed in the jackets and if films must be removed from the belt prematurely (as for the operating room) a note to that effect is inserted in the pocket in place of the loaned films. Under ordinary circumstances, films remain on display in the belts for 24 hours following which they go into the jackets for conventional filing. It is desirable that only trained clerks load and unload the belt-envelopes and that for subsequent viewing the fixed upper boxes be used.

DOUBLE BELT VIEWERS

For angiography, pneumo-encephalography and similar multiple film examinations and for the display of films at formal conferences the increased capacity of the double-belt Panoramascope outweighs its increased cost, the need of a librarian's

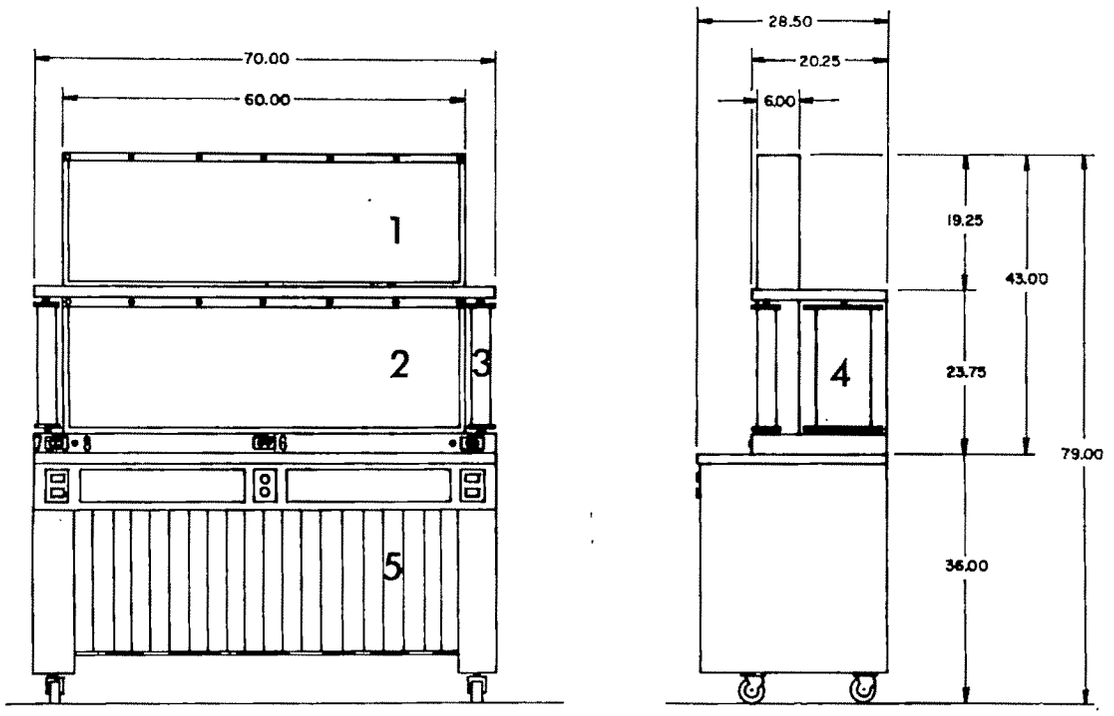


FIG. 2. Single-belt Panoramascope.

1. Upper deck; conventional 17 inch×60 inch view box.
2. Lower deck; belt-viewer.
3. Idler roller (one at either side).
4. Motor driven drum (one at either side). These drums alternately take up and pay out the Mylar Belt-Envelope thus driving its contained films across the face of the lower deck viewer.
5. Pigeon holes for jackets of cases being displayed in belt-envelope.
6. Main switch; illuminates view boxes and provides power to rectifiers which supply D.C. to motors, clutches, and brakes.
7. Slow-speed switch for motors which drive drums.
8. High-speed push button to double speed of belt.

stool for loading and unloading the upper belt and the fact that if a fixed view box is needed, it must be provided as an accessory.

Despite the increased capacity of the double-belt instrument (400 14 inch×17 inch films, and even more of smaller sizes) we find it desirable to have film clerks trim off unused edges of neuro-radiographs. This still further increases belt capacity, of course, but more particularly it allows the display of a lateral angiogram below and above it, in the same belt, the frontal mate throughout the series. Ordinary paper clips suffice to anchor the upper row films to the upper edge of the Mylar. With our present volume one double-belt viewer should be capable of holding all neuroradiology cases for a week thus making them constantly available to the radiology referring staff and ready for the weekly neuroradiology conference. Two or more additional double-belt viewers will be needed for weekly conferences with other services.

Our experience with the Philips Alternator is long and highly satisfactory and as a device for the sorting of films as they come from processors it is to be preferred to the Panoramascope. In our opinion, however, the latter is superior to the Alternator in ease and speed of loading, unloading and retrieving of films for viewing by successive crops of physicians during the



Fig. 3. Film clerk loading 14 inch×17 inch gastric film into belt of Panoramascope.

A double-belt instrument has a capacity of 400 14 inch×17 inch films and any of the 200 films in the 50 pockets of either belt can be brought into position for viewing in an average of less than 30 seconds and a maximum of less than 60 seconds.

Films remain in these transparent, easily retrievable files throughout the period of maximum interest, in most cases 24 hours.

day. In addition, it operates more quickly, requires less floor space, can be moved easily from room to room, and is much less expensive. We have had little experience with other types of European and American mass film viewers.

CONCLUSION

A suggested system for the mass viewing of the daily crop of radiographs in large teaching hospitals shifts from physicians to clerks all phases of the physical handling of X-ray films. It saves time for all concerned by holding current films in transparent, easily retrievable files until the period of maximum interest has passed.

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EDITORIAL

INTERVENTIONAL DIAGNOSTIC RADIOLOGY—A NEW SUBSPECIALTY

THE explosive growth of so-called special procedures in diagnostic radiology, made possible by the introduction of the Seldinger technique of catheterization, has masked and pushed into the background a progressively expanding new activity for the radiologist: interventional diagnostic radiology. When special procedures are used, the radiologist performs the technique of percutaneous introduction of contrast media into various systems of the body (arteriovenous, lymphatic, biliary, subarachnoid), or, occasionally, organs such as the kidney or liver and in the diagnosis of cysts. Like any traditional radiologist he also interprets the roentgenograms obtained during the procedure. In interventional radiology, however, the interpretation of roentgenograms of the procedure, if any are even obtained, is of only secondary importance. The principal factor lies in the intervention, which is controlled by fluoroscopy and which entails clinical judgment, technical skill, knowledge of and ability to avoid complications, as well as responsibility to the patient before, during, and after the procedure. If any films are to be obtained, they are exposed during the intervention, aiming to visualize its progress from step to step and, at the end, to document the final result and discover the possible complications.

The rapid, although unheralded, growth of interventional radiology may be attributed to the great versatility of fluoroscopic image-intensifying systems and the addition of television. Brilliant clarity of detail obtained in a lighted room, where aseptic technique can be maintained, with acceptable levels of radiation exposure for patient and radiologist, justifies the existence of this burgeoning activity and will result in its gain of momentum. Former attempts at interventional radiology have become dormant, mainly because of the great radiation hazard involved. Reduction of fractures and dislocations under direct fluoroscopic control had been virtually abandoned after the cumulative injury to the fluoroscoping manipulators.

The significant reduction in radiation exposure combined with the clarity and brilliance of the image and the improved maneuverability of the equipment, without sacrifice of safety to patient and physician, have more recently revived interventional radiology. Few procedures have been practiced even during the period of non-intensified conventional fluoroscopy, as for example reduction of intussusception by barium enema and removal of radiopaque foreign bodies from the bronchial system. These procedures survived only because their advantages proved to far outweigh the disadvantages.

Interventional radiology then is the growing body of manipulative procedures controlled and followed under direct intensified and/or televised fluoroscopic guide. It is performed by a physician skillful in radiologic techniques and experienced in the clinical problems. The procedures may be predominantly therapeutic or primarily diagnostic.

Examples of therapeutic procedures carried out by radiologists are numerous. Reduction of intussusception by barium enema[1] has already been mentioned. Ream-

[1] NORDENTOFT, J. M., and HANSEN, H. Treatment of intussusception in children: brief survey based on 1,838 Danish cases. (I. 1,042 cases 1928–1935. II. 796 cases 1944–1949.) *Surgery*, 1955, *38*, 311–319.

ing of thrombosed arteries of extremities to re-establish patency is being performed.[2] Distention arthrography for treatment of rigid joints[3] is a procedure showing promise. Re-establishment of patency of occluded tubes by reaming with guide wires has been described.[4] Similarly, crushing of small stones within the common duct with instruments introduced via the T-tube is feasible. Intrauterine fetal transfusion[5] is made possible by roentgenographic control of the needle. Precise placement of catheters in ultraselective catheterization of visceral arteries is opening new vistas for chemotherapy of tumors. Transjugular percutaneous cholangiography and percutaneous transhepatic cholangiography make decompression of the occluded biliary duct system possible before, or even in lieu of, laparotomy.[6]

The great advances in design of catheters have resulted in precision of their manipulation under fluoroscopic control. They offer feasibility of creation of deliberate shunts, as well as of closure of shunts, such as of intracardiac septal defects by patches. Nonoperative percutaneous drainage of subphrenic abscesses under fluoroscopic control with large tubes has been successful.[7] Antibiotics can be introduced through such tubes. Diagnostic interventional radiologic procedures are employed for biopsies of pulmonary nodules,[8] and intestine, as when a Crosby capsule is used. Most of the procedures mentioned are being performed or are being developed by radiologists, or with the help of radiologists as members of the team.

The question may well be asked whether interventional radiology is the rightful domain of the radiologist. Is versatility with the visualizing apparatus sufficient reason to entrust to the radiologist the performance of these procedures? The fact is undeniable that radiologists are performing many of these procedures and are primarily interested in, and responsible for, the development of others. Selective catheterization and the presently performed "special procedures" became the domain of radiologists because of interest and perseverance in the development of skill and their willingness to learn in detail and gain experience of the clinical aspects of the subspecialty (including physiology). Training, skill, clinical knowledge, and experience are also needed for performance of interventional radiology. Subspecialization and learning of the basic skills in performance of the procedure and of the immediate possible complications may well entail obligatory training in surgical techniques. The patients must be followed carefully and responsibility must be assumed faithfully. The radiologist's interest in the performance of interventions of this type will ensure continued development of apparatus such as the C-arm or stereo-television fluoroscopy, which are necessary for progress, as well as safer and more precise approaches. Our colleagues, the surgeons and internists, will undoubtedly cooperate either as members of the team or as teachers of their skills to advance interventional radiology.

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[2] Dotter, C. T., and Judkins, M. P. Percutaneous transluminal treatment of arteriosclerotic obstruction. *Radiology*, 1965, *84*, 631–643.

[3] Anden, L., and Lundberg, B. J. Treatment of rigid shoulders by joint distention during arthrography. *Acta orthop. scandinav.*, 1965, *36*, 45–53.

[4] Margulis, A. R., Newton, T. H., and Najarian, J. S. Removal of plug from T-tube by fluoroscopically controlled catheter: report of case. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1965, *93*, 975–977.

[5] Liley, A. W. Intrauterine transfusion of foetus in haemolytic disease. *Brit. M. J.*, 1963, *2*, 1107–1109.

[6] Hanafee, W. N., and Weiner, M. L. Transjugular percutaneous cholangiography. Presented at the Fifty-second Annual Meeting of the Radiological Society of North America, Chicago, 1966.

[7] Najarian, J. S., and Margulis, A. R. Unpublished data.

[8] Lauby, V. W., Burnett, W. E., Rosemond, G. P., and Tyson, R. R. Value and risk of biopsy of pulmonary lesions by needle aspiration: twenty-one years' experience. *J. Thoracic & Cardiovasc. Surg.*, 1965, *49*, 159–172.

NEWS ITEMS

THE AMERICAN BOARD OF RADIOLOGY

The American Board of Radiology wishes to announce the institution of a written examination to be given for the first time during the latter half of June 1968. This is to be given in various centers over the country and all residents having completed three years of approved training as of June 30, 1968 will be eligible to take the examination. Passing of the written examination will be a prerequisite to taking the oral examination. The fourth year of further training or practice presently required will still be mandatory.

Applications for the written examination or either of the oral examinations (June or December) *in any given* year must be filed *before* January 1 of the year in which the examination is given.

The present examination fee of $150.00 will, as of July 1, 1967, be increased to $200.00. This fee, however, will cover both the written and oral examinations where both are required. *Candidates eligible for the oral examination in June 1968 will not be required to take the written examination.* All re-examination fees will be increased from $75.00 to $100.00 as of the above date.

The Fall 1967 examination is to be held at the Statler Hilton Hotel, Dallas, Texas, December 4–8, inclusive; the deadline for filing applications is June 30, 1967.

The Spring 1968 examination will be held at the Fontainebleau Hotel, Miami Beach, Florida, June 10–14, inclusive; the deadline date for filing applications is December 31, 1967. *Deadline for filing for the written examination in June 1968 or the oral examination in December 1968 is December 31, 1967.*

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE

NBS High Energy Electron Beam Dosimetry Program

Following discussions with the Subcommittee on Radiation Dosimetry (SCRAD) of the American Association of Physicists in Medicine, the National Bureau of Standards (NBS) has agreed to undertake a nation wide check on the uniformity of high energy electron beam calibrations for medical institutions. This procedure is to be subject to NBS administrative approval and is to be carried out on a reimbursable basis.

The check will involve the use of Fricke dosimeters supplied by NBS. Members of a participating institution will insert this dosimeter into a cavity of suitable dimensions in a phantom furnished by the institution and constructed according to the guidelines given in "Protocol for Dosimetry of High Energy Electrons" published in *Physics in Medicine and Biology* (1966, *11*, 505). The participating institution will irradiate the dosimeter in the phantom to between 5,000 and 8,000 rads, using electrons of energies between 5 and 50 mev. The dosimeters may be irradiated either at two different energies, or at two different dose levels for one energy.

A base price, as yet to be determined, will be charged per uniformity check of two irradiated dosimeters together with two controls. Extra irradiations can be analyzed for an additional fee. NBS hopes that each participant will be able to make a commitment for four checks during the first year.

NBS is undertaking these uniformity checks on a temporary basis, anticipating that an absolute calibration service based on absorbed dose calorimetry will be established eventually. To assist the NBS in establishing interest, the American Association of Physicists in Medicine is requesting all persons who may be willing to subscribe to the basic service for a one year period to notify Dr. Margarete Ehrlich, Physicist, Dosimetry Section, National Bureau of Standards, Washington, D. C., 20234. It is anticipated that the first uniformity check would take place about July, 1967, with

three subsequent checks during the year ending July, 1968.

Technical questions about the "Protocol for Dosimetry of High Energy Electrons" are welcome and should be directed to the Chairman of the Subcommittee on Radiation Dosimetry, Dr. John S. Laughlin, Department of Medical Physics, Memorial Hospital, 444 East 68th Street, New York, New York, 10021.

The Subcommittee on Radiation Dosimetry believes that this opportunity is a substantial step forward in assuring consistent absorbed dose uniformity on a nation wide basis. Although exposure measurements of certain ionizing radiations have long been available from NBS at energies up to 1.25 mev., this is the first time that absorbed dose checks for energetic electrons have ever been offered to the scientific community.

NINTH INTER-AMERICAN COLLEGE OF RADIOLOGY

As already announced in the November, 1966 issue of this Journal, the Ninth Inter-American Congress of Radiology will take place in Punta del Este, Uruguay, December 6–12, 1967. Those who wish to submit any papers at this Congress should contact the Secretary, Dr. Helmut Kasdorf, Casilla de Correo No. 930, Montevideo, Uruguay.

The Congress will have some predetermined "themes" (see p. 762, Nov., 1966 issue of this Journal), but papers outside of the themes will also be acceptable.

The Lee Kirkland Group Travel Service, Inc., 3545 Broadway, Kansas City, Missouri 64111, will make arrangements for a charter flight for the convenience of those wishing to attend the Congress.

As usual, the American College of Radiology will call an Extraordinary Ceremonial Session to invest Honorary Fellows in Uruguay.

The official organ of the Inter-American College of Radiology is the *Revista Interamericana de Radiología*, ably edited by Dr. Guillermo Pezet, enthusiastic editor, Av. Petit Thouars 192, Lima, Perú, who exerted a great effort in improving the scientific and technical quality of its publication.

The Counselor for the United States to the Inter-American College of Radiology is Juan A. del Regato, M.D., Penrose Cancer Hospital, 2215 North Cascade Avenue, Colorado Springs, Colorado 80907.

SYMPOSIUM ON HIGH ENERGY RADIATION THERAPY DOSIMETRY

The American Association of Physicists in Medicine (AAPM) is sponsoring a Symposium on High Energy Radiation Dosimetry, June 15–17, 1967 at the New York Academy of Sciences in New York. The Symposium starts Thursday morning and runs until Saturday noon. It is intended to cover the major aspects of high energy radiation therapy dosimetry ranging from fundamental considerations through problems of application.

This Symposium is aimed to satisfy a need in the high energy radiation therapy field and follows the publication of the electron beam protocol by the AAPM and the current high energy x-ray protocol.

Papers will be presented covering: fundamental aspects of the absorption of high energy x-rays and electrons; energy calibration theory and practice; problems and experience in the measurement of absorbed dose; experience in intercomparisons between institutions; an extensive discussion of treatment planning procedures; a session on correlation of biologic effect and dosimetry for high energy electrons; and concludes with a session on developments in computer analysis and display. Both invited and contributed discussions will be obtained.

Although most of the speakers will be from within the AAPM, speakers already obtained from other than AAPM membership include Dr. Dietrich Harder of Germany; Dr. Martin Berger of the NBS; Dr. David Greene of Manchester; Dr. Wolfgang Pohlit of Germany; Dr. Herbert Attix of the Office of Naval Research; Dr. Jean

Dutreix of France; and Dr. Benno Markus of Germany.

Additional speakers and discussants are desired and will be sought. The fundamental objective of this Symposium is to provide information to all medical physicists concerned with high energy radiation therapy as to both the theory and basic procedures in the measurement of energy, absorbed dose, as well as the production of realistic treatment plans. The Symposium will be published by the New York Academy of Sciences in a separate volume of their proceedings.

The Symposium Organizing Committee consists of John S. Laughlin, Department of Medical Physics, Memorial Hospital, New York; Lawrence H. Lanzi, Department of Radiology and Argonne Cancer Research Hospital, the University of Chicago, Chicago; Robert J. Shalek, Department of Medical Physics, M. D. Anderson Hospital, Houston; and Ralph N. Worsnop, Department of Radiology, University of California Medical Center, San Francisco.

EUROPEAN CANCER MEETING

A European Cancer meeting supported by the Union Internationale Contre le Cancer and organized by Institut für Experimentelle Krebsforschung der Universität Wien, Chester Beatty Research Institute–Institute of Cancer Research–Royal Cancer Hospital, London, in cooperation with Wiener Medizinische Akademie will be held at Wiener Hofburg, Kongresszentrum, Wien 1/Austria, July 3–5, 1967.

A very outstanding program has been arranged. The official languages will be German, English and French.

A preliminary meeting is to be held with the intention of founding an European Federation for Cancer Research. Each country is invited to nominate a delegate with powers of decision, so that the points of view of all interested parties might be considered.

Further information may be obtained from Garber Travel Service, 1406 Beacon Street, Brookline, Massachusetts.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Notes on Radiological Emergencies. By George Ansell, M.D., R.R.C.P., F.F.R., D.M.R.D., Consultant Radiologist, Liverpool Regional Hospital Board, Liverpool, England. Revised reprint. E. & S. Livingstone, Ltd., Edinburgh, 1966.

Prepared in a handy looseleaf, wall hanging calendar form, this publication contains a concise listing of the major emergencies which occur in a Department of Radiology. These are carefully classified and described, giving the significant diagnostic signs and the steps to be taken in the treatment of each.

There is a list of the various agents and procedures used in roentgenologic examinations, the system examined and the complications most likely to accompany each. Among the causes of major emergencies are the use of contrast agents; anesthesia, both local and general; cardiac catheterization; pneumography; coronary disease; and electric shock. Reactions may involve the cardiovascular, respiratory or central nervous system or may present manifestations of an allergic nature.

A separate table lists each of these with the procedure to be taken, step by step, with helpful diagrams and charts.

For ready reference this may be conveniently placed on the wall in one or more rooms in the Radiology Department, where contrast studies and special procedures are performed.

William H. Shehadi, M.D.

BOOKS RECEIVED

Skull Radiography: a Simplified System. By Joseph Selman, M.D., Clinical Assistant Professor of Radiology, University of Texas, Southwestern Medical School; Director, School for X-ray Technicians, Mother Frances Hospital, Medical Center Hospital; Chief of Radiology, Mother Frances Hospital; Attending Radiologist, Medical Center Hospital; Consultant in Radiology, East Texas Tuberculosis Hospital, Tyler, Texas. Cloth. Pp. 213, with many illustrations. Price, $11.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1966.

The Adhesions of a Traumatized Tendon Formed under the Effect of Thyrotropin and Somatotropin: Experimental Studies by Physical and Histoquantitative Measurements. By Henry Brummer. Paper. Pp. 116, with some illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 89, Munksgaard, Copenhagen, 1966.

Motion of the Lumbar Spine with Special Reference to the Stabilizing Effect of Posterior Fusion: an Experimental Study on Autopsy Specimens. By Svante D. Rolander. Paper. Pp. 114, with some illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 90, Munksgaard, Copenhagen, 1966.

Biophysikalische Probleme der Strahlenwirkung. Jahrestagung der Deutschen Gesellschaft für Biophysik am 23–24 April, 1965, Homburg/Saar. Forward by Prof. Dr. rer. nat. H. Muth. Paper. Pp. 191, with 114 illustrations. Price, DM 29.70. Georg Thieme Verlag, Stuttgart. In U. S. A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1966.

Clinical Uses of Whole-Body Counting. Proceedings of a Panel on the Clinical Uses of Whole-Body Counting, held in Vienna, June 28–July 2, 1965. Paper. Pp. 291, with some illustrations. Price, $6.00. International Atomic Energy Agency, Vienna, 1966. In U. S. A. and Canada, International Publications, Inc., 319 East 34th Street, New York, N. Y., 1966.

New Concepts in Gynecological Oncology. Edited by George C. Lewis, Jr., M.D., Professor and Chairman; W. Budd Wentz, M.D., Research Assistant Professor; and Ronald M. Jaffe, M.D., Senior Instructor of the Department of Obstetrics and Gynecology, Hahneman Medical College and Hospital, Philadelphia, Pa. Cloth. Pp. 466, with 197 illustrations. Price, $20.00. F. A. Davis Company, 1914–16 Cherry Street, Philadelphia, Pa., 1966.

Disorders of the Respiratory Tract in Children: by 29 Authorities. Edited by Edwin L. Kendig, Jr., M.D., Professor of Pediatrics, Medical College of Virginia; Director of Child Chest Clinics, Medical College of Virginia Hospitals, Richmond, Va. Cloth. Pp. 834, with many illustrations. Price, $26.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa., 1967.

Bone Tumors: General Aspects and Data on 3,987 Cases. Second edition. By David C. Dahlin, M.D., Consultant, Section of Surgical Pathology, Mayo Clinic; Professor of Pathology, Mayo Graduate School of Medicine, University of Minnesota, Rochester, Minn. Cloth. Pp. 285, with many illustrations. Price, $16.00. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1966.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual Meeting: Washington-Hilton Hotel, Washington, D. C., Sept 26–29, 1967.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Fernando G. Bloedorn, Division of Radiotherapy, University of Maryland Hosp., Baltimore, Md. 21201. Annual meeting: Royal York Hotel, Toronto, Ont., Canada, May 29–31, 1967.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Nov. 26–Dec. 1, 1967.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting to be announced.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit, Mich. 48201. Annual meeting: Atlantic City, June 18–22, 1967.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.

The Spring 1967 examination will be held at the Pittsburgh Hilton Hotel, Pittsburgh, Pennsylvania, June 5–9, inclusive. The deadline for filing applications for this examination was December 31, 1966.

The Fall 1967 examination will be held at the Statler Hilton Hotel, Dallas, Texas, December 4–8, inclusive. The deadline for filing applications is June 30, 1967.

The Spring 1968 oral examination will be held at the Fontainebleau Hotel, Miami Beach, Florida, June 10–14, inclusive. The deadline for filing applications is December 31, 1967. Candidates eligible for this examination will not be required to take the written examination.

The first written examination will be held the latter half of June 1968 in various centers of the country for all residents having completed 3 years of approved training as of June 30, 1968. Deadline for filing for this examination and the oral examination of December 1968 is December 31, 1967.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo. 80907.

AMERICAN SOCIETY FOR DIAGNOSTIC ULTRASOUND
Secretary, Dr. Charles C. Grossman, 552 N. Neville St., Pittsburgh, Pa. 15213.

TWELFTH INTERNATIONAL CONGRESS OF RADIOLOGY
President, Dr. Kempo Tsukamoto, 9-1, 4-chome, Angewa, Chiba, Japan. Meeting: Hotel New Otane, Tokyo, Japan, Oct. 6–11, 1969.

NINTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907.
President, Dr. Leandro Zubiaurre, Montevideo, Uruguay. Meeting: Hotel San Rafael, Punta-del Este, Uruguay, Dec. 6–12, 1967.

INTER-AMERICAN COLLEGE OF RADIOLOGY
President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

ARIZONA RADIOLOGICAL SOCIETY
Secretary-Treasurer. Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meetingsix months later.

ARKANSAS CHAPTER OF AMERICAN COLLEGE OF RADIOLOGY
Secretary-Treasurer, Dr. William J. Rhinehart, St. Vincent Infirmary, Little Rock, Ark. 72205.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary-Treasurer, Dr. Stanley Rogoff, Department of Radiology, University of Rochester Medical School, Rochester, New York 14620. Annual meeting: Temple University School of Medicine, Philadelphia, Pa., May 12–13, 1967.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Colonel Kurt Harrell, Landstuhl Army Medical Center, Landstuhl, Germany. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. R. John Gould, 441 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Arthur Lieber, University of Kentucky, University Hospital, Lexington, Kentucky. Meets quarterly.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Robert L. Pinck, Long Island College Hospital, 340 Henry St., Brooklyn, N. Y. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Victor A. Panaro, 42 Burroughs Drive, Buffalo, N.Y. 14226. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Friday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:00 NOON.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert A. Bornhurst, State Univ. Hospital, 750 E. Adams St., Syracuse, N. Y. 13210. Meets first Monday each month, October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Ollie E. Southard, 2787 Tudor Rd., Columbus, O. 43209. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Fredric D. Lake, 2548 N. Lakeview Ave., Chicago, Ill. 60614. Meets second Thursday of each month, October to April, except December, at the Pick-Congress Hotel at 8:00 P.M.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Cleveland Radiological Society
Secretary-Treasurer, Dr. Theodore J. Castele, 18869 Canyon Rd. Parkview Park, Ohio 44126. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

Colorado Radiological Society
Secretary, Dr. George F. Wertz, 1801 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, John S. Alexander, 1217 W. Cannon, Ft. Worth, Tex. Meets monthly, third Monday, at Southwest International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Radiological Society
Secretary, Dr. Tom H. Piatt, 12 Camino Encinas, Orinda, Calif. 94563. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. T. F. Haase, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

Florida Radiological Society
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

Georgia Radiological Society
Secretary, Dr. Al Rayle, Jr., 938 Peachtree St., N. E., Atlanta, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Miami Radiological Society
Secretary-Treasurer, Dr. Arthur R. Miller, North Miami General Hospital, 1701 N.E. 127th St., North Miami, Fla. Meets monthly, third Wednesday at 8:00 P.M., at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, John W. Fries, 3520 Chippewa St., St. Louis, Mo. 63118.

Hawaii Radiological Society
Secretary-Treasurer, Dr. Donald Ikeda, Kuakini Hospital, 347 N. Kuakini St., Honolulu, Hawaii 96817. Meets third Monday of each month at 7:30 P.M.

Houston Radiological Society
Secretary, Dr. Zoltan Petrany, 1200 Moursond Drive, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Horne, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter, American College of Radiology
Secretary-Treasurer, Dr. Robert H. Greenlaw, Dept. of Radiology, Univ. of Kentucky Med. Ctr., Lexington, Ky. Meets semiannually.

Kentucky Radiological Society
Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Samuel Gelband. Meets second Tuesday of the month in February, April, June, October and December.

Los Angeles Radiological Society
Secretary, Dr. Norman Zheutlin, 8720 Beverly Blvd., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society
Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Waterville, Me. Meets in June, September, December and April

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building. Baltimore, Md.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Indiana. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Donald P. Babbitt, 1700 W. Wisconsin Ave., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Edward A. Peterson, 572 Lowry Medical Arts Bldg., St. Paul, Minn. Meets twice annually, fall and winter.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

Missouri Radiological Society
Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nebraska State Radiological Society
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month,

October through May, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. William G. McPheron, Hobbs, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society
Secretary, Dr. Arnold L. Bachman, Francis Delafield Hosp., 99 Fort Washington Ave., New York, N. Y. 10032. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Meeting: Waldorf Astoria Hotel, N. Y., April 27–29, 1967.

North Carolina Chapter of ACR. *Secretary-Treasurer*, Dr. Ira Bell, Hickory, N.C. Meets with the Medical Society of N.C., at Southern Pines, N.C., May 23, 1967.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. Robert J. Olson, 1240 8th Ave., Williston, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary-Treasurer, Dr. John Turner, 1215-28th St., Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Mortimer Lubert, Mt. Sinai Hospital, Cleveland, Ohio. Annual meeting to be announced.

Oklahoma State Radiological Society
Secretary, Dr. Robert Sukman, 1200 N. Walker, Oklahoma City, Okla. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. George W. Logan, 301 Newport Blvd., Newport Beach, Calif. Meets fourth Tuesday of every month at Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. Irving J. Horowitz, 2311 N.W. Northrup Str., Portland, Ore. 97210. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Willis Taylor, 1118 9th Ave., Seattle, Washington. Annual meeting to be announced.

Pennsylvania Radiological Society
Secretary, Dr. T. Frederick Weiland, 619 Ridgeway Ave., Grove City, Pa. Annual meeting to be announced.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Robert N. Berk, 9100 Babcock Blvd., Pittsburgh, Pa. 15237. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

Radiological Society of Connecticut, Inc.
Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450 Chapel St., New Haven 11, Conn. Meetings are held quarterly.

Radiological Society of Greater Cincinnati
Secretary, Dr. Harold N. Margolin, 6159 Tulane Road, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Lester W. Eavenson, 2700 Napoleon Ave., New Orleans 15, La. Meets semiannually, during Louisiana State Medical Society meeting and 6 months later.

Radiological Society of New Jersey
Secretary, Dr. John W. Marquis, 12 Hawthorne Ave., East Orange, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island
Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Gerald M. McDonnel, U.C.L.A. Medical Center for Health Sciences, Los Angeles, Calif. 90024. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Irving B. Joffe, Rochester General Hospital, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting: Brown Palace, Denver, Colo., Aug. 17–19, 1967.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles P. Hyslop, 7901 Frost St., San Diego 22, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. H. Joachim Burhenne, Children's Hospital and Adult Medical Center, 3700 California St., San Francisco, Calif. 94119. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco, Calif. 94118.

Santa Clara County Radiological Society
Secretary, Dr. Bill G. Karras. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Gregory T. Henesy, 915 19th St., N. W., Washington, D. C. 20006. Meets at Medical Soci-

ety Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. 32548. Annual meeting: Miami Beach, Fla., Nov. 13–16, 1967.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY
Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Washington Hilton Hotel, Wash., D.C., Sept. 25, 1967.

SOCIETY OF NUCLEAR MEDICINE
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Seattle, Washington, June 20–23, 1967.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Carleton J. Wright, 2015 Clarman Way, San Jose, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

SOUTHERN RADIOLOGICAL CONFERENCE
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting to be announced.

SOUTHWESTERN RADIOLOGICAL SOCIETY
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. E. K. Carter, Holston Valley Community Hosp., Kingsport, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting to be announced.

TRI-STATE RADIOLOGICAL SOCIETY
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Carlisle C. Smith, Salt Lake General Hospital, 2033 S. State St., Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. George G. Green, Morgantown, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Arnold Gerson, Medical Arts Bldg., Mt. Vernon, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. 53209. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY
Secretary, Dr. Ronald R. Lund, 240 W. 9th St., Casper, Wyo. Meets in fall with State Medical Society and in spring on call of President.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador.

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPÍA CUBANA
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A.C.
Coahuila No. 35, México 7, D. F.
Secretary-General, Dr. Armando L. Rodríguez
Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLÓGICA PANAMEÑA
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

SOCIEDAD RADIOLÓGICA DE PUERTO RICO
Secretary, Dr. José T. Medina, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY
Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May. Annual meeting: Central Hall and Caxton Hall, Westminster, London, S. W. 1., England, April 26–28, 1967.

CANADIAN ASSOCIATION OF PHYSICISTS, DIVISION OF MEDICAL AND BIOLOGICAL PHYSICS.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY
Secretary, Dr. B. V. Evans, 105 Northgate Bldg., Alberta, Canada. Meets second Tuesday of each month in various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting Guy's Hospital, London, June 23–24, 1967.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS IN IRELAND
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 p.m. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Maurice Dufresne, *Associate Honorary Secretary-Treasurer*, Dr. F. Robert MacDonald, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Skyline Hotel, Toronto, Canada, Feb. 28–March 5, 1967.

Montreal Radiological Study Club
Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie
Secretary General, Dr. Jacques Lespérance, 5415 Boul. L'Assomption, Montreal 26, P. Q., Canada. Meets every third Tuesday from October to April. Annual meeting: Oct. 12–14, 1967.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. T. P. Loneragan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 p.m. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Miguel Maric Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia
Secretary-General, Dr. Eduardo E. Navarrine, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Boliviana de Radiología
Secretary, Dr. Héctor Fernández Ferrufino, Casilla 1192, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Patricio Barriga, Casilla 13426, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary-General, Dr. Armando Uribe, Hospital Militar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary-General, Dr. Augusto Cáceres G. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologica del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Barranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedad de Radiología de El Salvador
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Luis F. Muro, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie
General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France.
General Secretary, Dr. H. Ludin, Department of Roentgenology, Basler Kinderspital, Basel, Switzerland. Annual Meeting: Basel, Switzerland, April 13–17, 1967.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

Scandinavian Association for Medical Radiology
Secretary-General, Dr. C-E. Unnérus, Hagalund-Tapiola, Havsvindsvägen 5 C., Finland. Annual meeting: Umeå, Sweden, 1967; Copenhagen, Denmark, 1968.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Juan Gomez Lopez, Villanueva, 11, Madrid 1. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid. Annual general meeting to be announced.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah I Diakarta, Indonesia

Iranian Radiological Society
Secretary, Dr. Issa Yaghmai, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

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ROENTGEN DIAGNOSIS

Head

Klumair, J. Über die Häufigkeit und Bedeutung des Falxknochens. (Frequency and significance of the falx bone.) *Radiol. Austriaca*, 1966, *16*, 221–226. (Address: Krankenhaus der Stadt Wien-Lainz, Röntgeninstitut, Wien XIII, Austria.)

The falx bone is not an uncommon finding in the adult skull. Nevertheless, its significance is still debated. Some authors believe that the falx bone is due to trauma or the spread of an inflammatory process of the nasopharynx. Even birth trauma with subdural hemorrhage, neuropathy and pachymeningitis have been made responsible for its development. All these pathogenetic considerations cannot be proved clinically or otherwise.

Comparative anatomy reveals that the falx bone can be regularly observed in the Australian bird *Ornithorrhynchus paradoxus* and occasionally also in other birds. Tentorial ossification frequently occurs in mammals whereby the posterior base of the falx also is involved. This ossification spreads anteriorly to the cribriform plate (crista Galli and crista frontalis) in 5 per cent of the mammals.

Four thousand roentgenograms of the skull, comprising 1,840 males and 2,160 females, form the basis of the present statistical evaluation. Ossification of the falx was observed in 168 males (9.13 per cent) and 135 females (6.25 per cent) for a total of 303 (7.57 per cent). Fifty per cent of the affected patients were 55 to 65 years old. Follow-up studies in some cases revealed that the appearance of the ossification remained unchanged during many years of observation. In 272 children, 3 years of age and older, the frequency of the falx bone was only 5.8 per cent.

It is the author's belief that the falx bone represents a developmental vestige of a bony septum between the two cerebral hemispheres (regressive variant with a weak penetrant).—*Ernest Kraft, M.D.*

Birkner, R., and Lagemann, K. Ausgedehnte Verkalkungen bei Pachymeningitis haemorrhagica interna und Haematoma subdurale: über einen Fall von "Panzerhirn." (Extensive calcifications in hemorrhagic internal pachymeningitis and subdural hematoma: concerning a case of "armored brain.") *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1966, *105*, 377–381. (Address: Röntgeninstitut und Strahlentherapeutische Klinik des Städtischen Krankenhauses Moabit, Turmstr. 21, 1 Berlin 21, Germany.)

The case of a 53 year old man is reported in which routine skull roentgenograms disclosed symmetric calcium shells completely wrapping both cerebral hemispheres. The roentgen appearance is likened to an "armored" brain or "Panzer" brain derived from the term "armored" or "Panzer" heart. The man was referred for evaluation of a disability. The history revealed frequent small seizures with slight head injuries when the patient was 8 to 12 years old. After this period, he was symptom free for 35 years. During the past 2 years, he suffered from short spells of unconsciousness, memory slips and Parkinson-like trembling.

Repeated small traumas can cause progressive dural hemorrhages and internal hemorrhagic pachymeningitis. Subdural hemorrhages can also be due to degenerative-hyperplastic disease of the dura. Most likely, both factors play a role in the development of the dural calcifications. The authors doubt that the head injuries during the patient's childhood are responsible for the extensive dural calcifications because of the symptom free interval of 35 years.—*Ernest Kraft, M.D.*

McHugh, Paul R. Hydrocephalic dementia. *Bull. New York Acad. Med.*, Oct., 1966, *42*, 907–917. (From: Department of Neurology, Cornell University Medical College, New York, N. Y.)

A lesion causing hydrocephalus in an adult can produce an insidiously progressive dementing illness. This dementia can be present without a significant cerebrospinal fluid pressure elevation as measured by lumbar puncture. Furthermore, a lesion causing partial obstruction to fluid can permit air to pass during pneumoencephalography, outlining a symmetrically dilated ventricular system above. Since any brain atrophy such as Pick's or Alzheimer's disease can also cause progressive dementia with normal spinal fluid pressure and symmetrically dilated ventricular system, the diagnosis of hydrocephalus is occasionally difficult. Differentiating between hydrocephalus and atrophy is of obvious importance because of the effectiveness of neurosurgical shunting in hydrocephalus.

A case report is presented illustrating clinical and roentgenologic findings differentiating hydrocephalic dementia from brain atrophy. A 49 year old man with progressive dementia, apathy and leg weakness had a pneumoencephalogram which showed only dilatation of lateral ventricles. Spinal fluid pressure was very minimally elevated. The diagnosis of presenile brain atrophy was made but later questioned on the basis of a very fluctuating clinical course. Carotid arteriography and repeat pneumoencephalography established the presence of obstructive hydrocephalus and illustrated the important neuroradiologic differentiation.

If a specific obstructing lesion is demonstrated on pneumoencephalography, the diagnosis of hydrocephalus is a certainty; however, it is not unusual for these lesions to elude even careful search. A num-

ber of indirect features may then be helpful in differential diagnosis.

Gross ventricular dilatation is seen characteristically early in the clinical course of hydrocephalic dementia. Ventricular enlargement is modest in brain atrophy unless the clinical course extends over many years. It may be difficult to introduce air into the cortical subarachnoid space in hydrocephalus, but in brain atrophy dilated sulci are usually demonstrated readily.

Carotid arteriography can evaluate the significance of ventricular dilatation when no obstruction has been demonstrated on the air study. The concept hydrocephalus "ex vacuo," implies that ventricular dilatation in brain atrophy is a result of a wasting of brain tissue. Thus, although the ventricles occupy greater space, they do not push away structures lying on the surface of the brain. The stretching of the pericallosal arteries seen around obstructively dilated lateral ventricles, is not present in the atrophically enlarged ventricles.

This last point was the deciding factor in this case workup and prompted the definitive re-examination by air study, at which time a tiny mass was found at the junction of third ventricle and aqueduct. Ventriculocisternostomy followed by radiation therapy resulted in striking clinical improvement.—*Rosalind H. Troupin, M.D.*

Hogan, Patrick A., and Woolsey, Robert M. Hydrocephalus in the adult. *J.A.M.A.*, Oct. 31, 1966, *198*, 524–528. (Address: Dr. Woolsey, 1221 S. Grand Boulevard, St. Louis, Mo.)

Chronic headache, gait disturbance, and dementia may be the presenting symptoms in hydrocephalus in the adult. Pneumoencephalography is necessary to substantiate the diagnosis and ventriculo-atrial shunt usually reverses the symptoms even though they may have been of many years duration. Hydrocephalus is due to a block between the site of cerebrospinal fluid formation in the choroid plexus of the lateral, third and fourth ventricles, and the site of absorption in the subarachnoid spaces. The causes of such a block are numerous and include: tumors of the third and fourth ventricle or of the brain stem and cerebellum; aqueduct stenosis; leptomeningeal fibrosis due to meningitis; subarachnoid hemorrhage, etc.

The technique of pneumoencephalography should be standardized so that an attempt to fill the cerebral subarachnoid spaces is included. This will differentiate the "atrophic brain" from the purely hydrocephalic brain by showing dilatation of cortical sulci as well as ventricular enlargement.

Four case reports are given, illustrating the various manifestations of hydrocephalus in the adult. Case I gave a history of 7 years of occipital headache. Following operation and placement of a Holter valve, the patient had no headache for a period of 7 months. Hydrocephalic paraplegia in Case II and III was relieved by ventriculo-atrial and subarachnoid-peritoneal shunt procedures, respectively, but follow-up pneumoencephalography revealed no decrease in ventricular size in Case II and Case III continued to have headache.

Dementia without other neurologic symptoms has been reported by others and Case IV is to be treated by shunt because of dementia and hydrocephalus developing after subarachnoid hemorrhage from a cerebral artery aneurysm which was clipped 10 days after onset of bleeding.—*Richard E. Kinzer, M.D.*

Argires, James P., and Nelson, John. Pituitary apoplexy: review of the literature and two case reports. *South. M. J.*, July, 1966, *59*, 785–789. (From: Department of Neurosurgery, University of Alabama Medical Center, Birmingham, Ala., and Department of Neurology, University of Tennessee College of Medicine, Memphis, Tenn.)

Two cases of pituitary apoplexy with good outcomes are reported along with a review of the literature.

Pituitary adenomas occasionally tend to undergo "spontaneous" vascular changes such as massive hemorrhage or infarction, producing the clinical syndrome of pituitary apoplexy. This is an unusual presentation for pituitary adenomas.

Clinical signs include marked visual loss or extraocular palsies of rapid onset. The clinical symptoms consist of sudden onset of headache, nausea and vomiting, nuchal rigidity, fever, drowsiness, confusion or coma, dysplopia, ophthalmoplegia, amblyopia and rarely hemiparesis. Secondary signs of acute panhypopituitarism frequently complicate the picture. An enlarged or eroded sella turcica on skull roentgenograms was reported in almost all instances and cerebral angiography may show the presence of a pituitary mass. Xanthochromic or bloody cerebrospinal fluid was a frequent finding along with pleocytosis.

Cerebral angiography may be necessary to exclude an aneurysm of the internal carotid artery producing a similar clinical picture.

Acute hemorrhage occurring with known tumors receiving radiation therapy was reported in only 8 cases in the review of the literature.

Early surgical intervention may be necessary to save vision, to prevent pressure on adjacent vital structures and to relieve increased intracranial pressure.—*Lawrence H. Gold, M.D.*

Sutton, David, and Davies, E. Rhys. Arch aortography and cerebrovascular insufficiency. *Clin. Radiol.*, Oct., 1966, *17*, 330–345. (From: Radiological Department, St. Mary's Hospital, London, W.2, England.)

The authors have performed arch aortography in over 700 patients. In 330 of these, all with a clinical

diagnosis of cerebrovascular insufficiency, the arch aortograms have been analyzed in an effort to assess the functional importance of extracranial vascular disease.

The anatomic variation seen most often was a common origin for the innominate and the left common carotid artery. The left vertebral artery arises from the aortic arch in 5–6 per cent of patients. A patient with a proximal left subclavian occlusion will be saved from a subclavian steal if the vertebral artery is anomalous.

The patients with extracranial pathology were divided in the following 4 groups:

Group 1. In this group there were 157 cases with localized stenosis or occlusion of at least one extracranial artery. The commonest site of carotid artery occlusion was immediately distal to the origin of the internal carotid artery. Carotid stenosis was found primarily at the origins of either the internal carotid or the common carotid arteries. Vertebral occlusion was always at the origin of the artery, and vertebral stenosis most commonly occurred at this site. Both the carotid and vertebral systems were involved in 25 per cent of the cases.

Group 2. Subclavian steal. The 26 cases in this category form a separate group because of their unique hemodynamics. A common feature is the occlusion of the subclavian or innominate artery proximal to the origin of the vertebral artery, with consequent retrograde flow in the vertebral artery. Careful aortography is the only reliable way of making the diagnosis of subclavian steal.

Group 3. Simple atheroma. In 65 cases atheroma of the proximal parts of the major branches of the arch was found, without any evidence of occlusion or stenosis.

Group 4. No extracranial lesion. No evidence of an extracranial lesion could be found in 85 cases.

Theoretically the circle of Willis is a perfect collateral system. However, its potential is limited by the frequency of congenital anomalies. The most important ones are hypoplastic posterior communicating, or anterior cerebral arteries. Other important anomalies are the total absence of 1 vertebral artery and failure of fusion of the 2 vertebral arteries. The critical factors in determining whether or not symptoms occur are the hemodynamic state and the adequacy of the collateral pathways.

In conclusion, the authors state that the clinical symptoms are extremely difficult to interpret when multiple lesions are present.—*Samuel G. Henderson, M.D.*

Greitz, T., and Link, H. Aseptic thrombosis of intracranial sinuses. *Radiol. clin. et biol.*, 1966, *35*, 111–123. (Address: Prof Dr. T. Greitz, Head of Neuroradiological Department, Karolinska Sjukhuset, Stockholm 60, Sweden.)

Aseptic thrombosis of intracranial sinuses is a rare disease. It has been found in patients who are cachetic, in children with congenital heart deformities; in patients with head injuries acute severe right heart failure, diabetes mellitus, malignant blood disease, lung operations; or without any demonstrable coexisting disease.

Most cases of aseptic thrombosis of the intracranial sinuses have been diagnosed at autopsy.

The authors describe 2 patients with a favorable clinical course.

In 1 of these patients carotid arteriography demonstrated collateral circulation via superficial scalp veins and cervical vertebral veins to the contralateral jugular vein and from the cavernous sinus via the ophthalmic veins to the facial veins.

An argument against the use of carotid angiography in the investigation of sinus thrombosis is that only filling of the supratentorial veins on one side is obtained.

The authors feel that aortocervical angiography could be of value in such an investigation, since it visualizes all intracranial veins and sinuses, as well as the jugular veins.—*Forrest Arnoldi, M.D.*

Abramson, Allyn S. Ectopic submaxillary gland in the mandible: report of case. *J. Am. Dent. A.*, Nov., 1966, *73*, 1114–1116. (Address: 6363 Wilshire Boulevard, Los Angeles, Calif. 90048.)

Static or latent bone cysts located at the angle of the mandible have been previously explored and found in some cases to contain ectopic submaxillary gland tissue. In other cases, these cysts were devoid of any content. These lesions are usually asymptomatic and unassociated with the teeth.

In this report the author describes an asymptomatic lesion in the mandible in a different location. The lesion was in the right mandible in the region of a missing canine tooth. Removal was accomplished, after initial refusal, some 10 months later because of pressure symptoms. Pathologically the lesion was compatible with submaxillary gland. The etiology is postulated to be an embryonic cell abnormally placed in the mandible.

The point of this article is that this abnormal submaxillary tissue can appear elsewhere in the mandible in addition to the previously reported cases at the angle. Removal and pathologic evaluation are necessary for final diagnosis and differentiation from other mandibular lesions.—*George A. Kling, Captain, MC*

Menczer, Leonard F. The open-ended metal column for the dental x-ray machine. *J. Am. Dent. A.*, Nov., 1966, *73*, 1083–1089. (Address: Hartford Health Department, 56 Coventry Street, Hartford, Conn.)

The author, concerned about reducing radiation to the dental patient, designed open-ended metal columns for the dental X-ray machines in the Greater

Hartford Area. This entailed designing 8 different cones for the models in use. There were 286 practicing dentists using 359 x-ray machines.

The plastic cone currently in use is pointed and absorbs as well as transmits radiation. It produces considerable secondary radiation and scatter, has penumbra effect and with some types of machines, has anterior leakage.

The open-ended shielded device can reduce gonadal exposure by 50 per cent, eliminate penumbra and secondary radiation and reduce anterior leakage. This metal column requires better positioning thereby getting better parallelism of the primary beam with resultant better roentgenograms.

Several minor problems of adapting film holders, retraining the dentist and/or technicians in proper positioning and care with the new heavier column were encountered. The x-ray head and supporting arm of the unit had to be rebalanced. These problems were solved with little difficulty.

The author found acceptance of the new device to approach 100 per cent. The makers of dental equipment also seemed to accept this column well and the author feels hopeful that it will be generally accepted and promoted by the dental profession. —*George A. Kling, Captain, MC*

Neck and Chest

Barbaccia, F., and Calò, S. L'esame radiologico nella sindrome di insufficienza respiratoria del neonato immaturo (malattia della membrana ialina). (The radiologic examination of the syndrome of respiratory insufficiency of the premature newborn [hyaline membrane disease].) *Radiol. med.*, April, 1966, *52*, 324–333. (Address: Dott. Prof. Franco Barbaccia, Via Mac Mahon, 79, Milano, Italy.)

The authors have studied 60 premature infants aged from 1 to 10 hours and weighing from 1,000 to 2,500 gm. who presented clinical and roentgenographic findings of neonatal respiratory distress.

The roentgen findings present in all cases have been previously described and comprise: bilateral, irregular, diffuse granularity; changes suggesting atelectases, with or without demonstrable air bronchogram; enlarged mediastinum; pneumothorax; and changes in the volume of the thoracic cavity.—*A. F. Govoni, M.D.*

Adelman, A. G., Chertkow, G., and Hayton, R. C. Familial fibrocystic pulmonary dysplasia: a detailed family study. *Canad. M. A. J.*, Sept. 17, 1966, *95*, 603–610. (From: Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.)

This report demonstrates the previously described high familial incidence of idiopathic diffuse interstitial pulmonary fibrosis (Hamman-Rich disease), and the fact that this condition can be transmitted by a simple mendelian dominant gene.

The fact that immuno-globulins were elevated in most of the children and in 5 of the siblings, suggests an inherited aberration of the immune response in this family.—*John H. Harris, M.D.*

Drapanas, Theodore, Siewers, Ralph, and Feist, John H. Reversible poststenotic bronchiectasis. *New England J. Med.*, Oct. 27, 1966, *275*, 917–921. (From: Departments of Surgery and Radiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa.)

Reversible bronchiectasis was first described in 1935 by Findlay. He reported 2 cases in which bronchiectasis disappeared following the re-expansion of lobar atelectasis. Cases of atypical pneumonia have also resulted in reversible bronchiectasis.

The authors present a case of traumatic rupture of the left main stem bronchus secondary to closed chest trauma resulting in progressive stenosis of the bronchus. Two weeks after injury, cinebronchography revealed extensive cylindrical and saccular bronchiectasis of the atelectatic left lung.

One month after injury the stenotic area was resected and an end-to-end anastomosis of the left main stem bronchus was carried out.

Bronchograms 8 days after surgery showed improvement of the bronchiectasis. Repeat bronchograms 1 month after surgery revealed a normal tracheobronchial tree.—*George A. Miller, M.D.*

Witzleb, W., Sprössig, M., Anger, G., and Heidler, S. Respiratory disease due to *Mycoplasma pneumoniae*. *German Med. Monthly*, Sept., 1966, *11*, 345–348. (From: Department of Medical Microbiology and the Medical Clinic, Medical Academy, Erfurt, Germany.)

The term of "atypical pneumonia" is now used to denote any pneumonia in which the clinical picture deviates from the "typical pattern" seen in lobar and bronchopneumonia of bacterial origin. Atypical pneumonia may be caused by a variety of pathogens including bacteria, fungi, rickettsiae and viruses.

In a series of 164 hospitalized pneumonia patients, 16 were found to be seropositive to *Mycoplasma pneumoniae*. Among 21 other patients with respiratory complaints (bronchitis, tracheitis, rhinopharyngitis), 2 showed similar seropositive findings.

In the cases of pneumonia, no uniform clinical picture was found. The mycoplasmas are inhibited by tetracyclines in the usual doses, but are resistant to penicillin.—*George A. Miller, M.D.*

Marchi, B. Le manifestazioni polmonari del morbo di Behcet. (Pulmonary manifestations of Behcet's disease.) *Radiol. med.*, April,

1966, *52*, 314–323. (Address: Via Aringhieri, 2, Siena, Italy.)

The Behcet-Adamantiades syndrome is a rare variant of erythema multiforme. This syndrome or triple symptom complex, as it has been called, is rather frequent in countries bordering the Mediterranean Sea, although quite a few cases have been observed in Central Europe, the Scandinavian Countries, and the United States.

The syndrome is characterized by recurrent erosive lesions involving the eyes, the mucosa of the mouth and upper respiratory airways and the genitalia. Furthermore, the patient might present erythema nodosum or erythema multiforme. Males are most commonly affected and between the ages of 15 and 40 years. The disease has a chronic course and lasts for many years.

Many theories have been advanced on the etiology of the syndrome. Recently Nazzaro suggested, on the basis of histologic findings, that we could be dealing with a systemic lesion of vascular origin on an allergic-hyperergic basis, indicating therefore, an analogy between the syndrome of Behcet and the diseases of the collagen.

The case observed by the author is that of a man, 42 years of age, who presented all the classic symptoms of the triad and the classic erythema nodosum. Routine chest roentgenograms showed a few small, nonhomogeneous shadows of parenchymal infiltration in the supradiaphragmatic regions and, in particular, pronounced right hilar lymphadenopathy. The findings were confirmed by tomographic studies.

Only 4 cases, out of 17 reported in the literature in which pulmonary pathology was present, showed similar hilar lymphadenopathy.

In the opinion of the author the pulmonary findings should be considered part of the syndrome. The pathologic changes involve the trachea and main bronchi, and/or the paratracheal lymph nodes, or the alveoli.—*A. F. Govoni, M.D.*

Donohoo, C. M. Bronchopulmonary aspergillosis. *Australasian Radiol.*, Aug., 1966, *10*, 225–228. (Address: Radiological Registrar, Prince Henry's Hospital, Melbourne, Australia.)

Aspergillus is a saprophytic aerobic fungus, a regular inhabitant of the soil, and found predominantly in warm, damp climates.

The common portal of entry is the respiratory tract. The fungus, being aerobic, requires communication with the bronchial tree for growth. Aspergillus almost invariably involves the respiratory tract, it rarely disseminates to other organs.

Pulmonary aspergillosis may be classified as: (1) intracavitary aspergilloma, whose characteristic and classic radiologic appearances are well known, and therefore are not discussed; and (2) bronchopulmonary aspergillosis, which may be (a) primary, or (b) secondary.

The bronchopulmonary aspergillosis presents as a process with a tendency towards progression. The symptoms and radiologic picture of the acute form may closely simulate tuberculosis, bronchopneumonia or lobar pneumonia.

The primary type is quite uncommon and is mainly occupational, occurring in grain workers and pigeon breeders. Aspergillus may be found in the soil, grain and hay, and is also carried by pigeons and other birds. Radiographically this form may present as a patchy collapse and consolidation of migratory character due to plugging of bronchi by mycelia, mucus and fibrin, or sometimes as an acute severe pulmonary collapse. The changes may begin in the hili with diffuse enlargement of the hilar shadows and spread along the bronchi and vessels within the lung parenchyma. They may infiltrate an entire lung and sometimes involve the mediastinal lymph nodes, the superior vena cava or the myocardium.

The acute form may develop into a more or less generalized fibrosis and simulate bronchiectasis or it may heal leaving disseminated calcification and be confused with miliary tuberculosis.

Secondary aspergillosis may occur in bacterial bronchopneumonia, pulmonary infarction, bronchiectasis, tuberculosis and pneumoconiosis. However, it is far more commonly observed in a severe debilitating systemic disease such as leukemia or carcinoma.

A rising incidence of aspergillosis has been associated with the increased use of antimicrobial or adrenal steroid therapy, and antineoplastic drugs, most probably due to the creation of favorable conditions for the growth of the fungus.

The sputum culture of the fungus is difficult and unreliable, since a considerable variation in the staining qualities is noted.

Two unusual cases of secondary aspergillosis are described: one, a male aged 40 years with leukemia on vigorous drug therapy, who subsequently developed secondary aspergillosis in the form of multiple mycotic lung abscesses; and the other, a man, 50 years of age, with recurrent attacks of bronchopneumonia, who was treated with antibiotics, and then developed secondary infection by aspergillus.—*Stephen N. Tager, M.D.*

Knudson, Ronald J., Badger, T. L., and Gaensler, E. A. Eosinophilic granuloma of the lung. *Med. Thoracalis*, 1966, *23*, 248–262. (From: The Thoracic Services, Boston University, Boston, Mass.)

Eosinophilic granuloma of the lung was first described 15 years ago; since that time 75 cases have been reported. Ten cases have been seen over a 15 year period by the Thoracic Services of Boston

University and one is presented to illustrate some of the typical features.

The term "eosinophilic granuloma" was first applied to solitary bone lesions but cases were soon recognized with extraskeletal involvement of skin, thyroid, gastrointestinal tract and finally lung. It is considered one of the "histiocytoses-X" together with Letterer-Siwe and Hand-Schüller-Christian disease. The lungs may remain the only affected site, although some of these patients have diabetes insipidus indicating hypothalamic-hypophyseal involvement.

In the lung, the pathologic lesion is a patchy, nonencapsulated interstitial granuloma, with large, pale histiocytes and intermingled eosinophilic granulocytes. There is no true caseation, although some granulomas may have a peculiar central area of dissolution. Early lesions characteristically are arranged around blood vessels and there is often a distinct arteriolitis. Although the disorder is usually self-limited, in some instances involvement may become massive and progress to fibroblastic proliferation and extensive cystic degeneration or "honeycombing." It is to be stressed, however, that the "honeycombing" pattern is by no means pathognomonic.

Physiologic alterations in pulmonary function vary with the stage and severity of the disease and may correlate poorly with the roentgenographic findings. Breathing dynamics are usually normal. Some patients do demonstrate an "alveolar-capillary block syndrome" related to the arteriolar obliteration, lung destruction and cellular infiltration.

The roentgenographic abnormalities are quite variable and not diagnostic. In early cases there may be true miliary infiltration but more often coarse focal nodulation and reticulation are seen which may coalesce to form patchy densities. Apparent resolution of the lesion may actually be due to progressive fibrosis, contraction, and development of perifocal emphysema. Characteristically there is no mediastinal lymphadenopathy. Skeletal survey may reveal osteolytic skull and rib lesions. Spontaneous pneumothorax is such a sufficiently common complication, that its occurrence should alert one to the possibility of eosinophilic granuloma of lung.

The differential diagnosis of any diffuse or miliary lung disease should include eosinophilic granuloma. A negative occupational history, minimal symptoms, absence of toxicity and lack of hilar lymphadenopathy make the diagnosis more likely. The presence of bone lesions or diabetes insipidus is helpful, as is spontaneous pneumothorax.

Any evaluation of therapy in this disease is made difficult by a tendency toward spontaneous remission. Radiation therapy is ineffective in low doses, and in larger doses poses the danger of additional pulmonary fibrosis. Corticosteroids are currently advocated by most authorities.—*Rosalind H. Troupin, M.D.*

Janover, Murray L., Dreyfus, Jack R., and Skinner, David B. Azygography and lung cancer. *New England J. Med.*, Oct. 13, 1966, *275*, 803–808. (From: Departments of Radiology and Surgery, Harvard Medical School, and the Department of Radiology and the Surgical Services, Massachusetts General Hospital, Boston, Mass.)

Evaluating operability in patients with carcinoma of the lung remains a difficult problem. Despite a variety of preoperative investigations, the tumors of one-third of patients surgically explored prove to be beyond resectable limits. Roentgenographic visualization of the azygos vein provides an additional method of detecting mediastinal spread.

The authors present the Massachusetts General Hospital experiences with 120 cases.

Technique. After skin preparation and procaine infiltration, the tip of an 18 gauge spinal needle is introduced into the 9th or 10th rib marrow space on the side of the lesion. The patient is supine, and puncture is made in the mid-axillary line. The needle is connected to plastic tubing and following injection of 1 cc. of procaine a small test injection of renografin or hypaque is made, monitored fluoroscopically or by a Polaroid exposure; 20 cc. of contrast material is then injected by hand and near the end of the injection an anteroposterior dorsal spine roentgenogram is obtained. Only minimal discomfort is encountered and the authors have discontinued their former practice of demerol premedication. No significant complications have arisen.

Interpretation. The azygos vein is readily identified as normal, partially obstructed or totally obstructed. Normally, no collateral channels are seen, nor should there be retrograde flow down the ascending lumbar veins. In instances of complete block, resulting backpressure prevents the exact site of obstruction from being opacified.

Results. Azygography was employed in evaluation of 120 cases admitted with the presumptive diagnosis of lung cancer. During the course of this study the results of azygography were not used to influence therapy. The remainder of the preoperative workup included bronchoscopy, scalene biopsy, barium swallow, angiocardiography and skeletal survey. Eighteen patients were ultimately proven to have nonmalignant disease, and in 15 the azygograms were negative. Complete obstruction occurred in 1 patient with tuberculosis and extensive mediastinal fibrosis. Partial block was seen once in inflammatory lymphadenopathy and once in mediastinal neurofibroma.

Thirty-seven patients were obviously inoperable by virtue of phrenic or laryngeal nerve paralysis, caval obstruction or distant spread; 25 of these showed azygos obstruction—a higher yield than with any other single diagnostic measure.

Sixty-five patients were considered operable on the basis of other preoperative studies; 40 of these

proved to have resectable lesions and there were 3 false positive azygograms in the group; 20 proved to have unresectable lesions on exploration, and of these 10 had had an abnormal azygogram. All cases with abnormal venous angiocardiograms had azygos obstruction as well.

Azygography was found to be most accurate in cases where hilar lesions or lymphadenopathy were present. If a blocked azygos vein is the only sign of inoperability, radiation therapy and repeat azygography may permit reconsideration of surgical resection.—*Rosalind H. Troupin, M.D.*

Fred, Herbert L., Burdine, John A., Jr., Gonzalez, David A., Lockhart, Robert W., Peabody, Carroll A., and Alexander, James K. Arteriographic assessment of lung scanning in the diagnosis of pulmonary thromboembolism. *New England J. Med.*, Nov. 10, 1966, *275*, 1025–1032. (From: Departments of Medicine and Radiology, Baylor University College of Medicine and Ben Taub General Hospital, Houston, Texas.)

Scintillation scanning of the lungs is now being used in diagnosis of pulmonary thromboembolism. The authors have correlated the scanning with pulmonary arteriography in 73 cases of pulmonary and cardiovascular disorders of which 27 had pulmonary thromboembolism.

Of the 27 patients with pulmonary thromboembolism, 22 had decreased uptake of radioactivity over the regions of the lungs shown by arteriography to have intra-arterial occlusive lesions. One scan was normal in a patient with complete obstruction of the distal end of one segmental artery. Four patients with bilateral multiple lesions on arteriography had scans showing abnormalities more striking on one side.

Of the 46 patients with other lesions, most had abnormal scans which correlated with the abnormal areas on the roentgenographic studies. Lesions such as pulmonary fibrosis and bronchogenic carcinoma often appeared larger on the scans than on the roentgenograms. Patients with pneumonia had scans which correlated quite well with the roentgenograms. Ten patients had left ventricular failure and they all showed decreased radioactivity over one or both lung fields when the arteries were attenuated but patent.

Four of the 5 patients whose scans failed to accurately localize the pulmonary thromboembolism had large partially occlusive thromboemboli in one lung and complete occlusion in the other lung. This is due to increased pulmonary blood flow in the partially occluded vessels with a resultant normal scan on that side.

Normal scans may occur with small lesions in close proximity to the diaphragm and when the pulmonary blood is reduced equally and diffusely. This appearance has been shown in pulmonary fibrosis and idiopathic pulmonary hypertension.

Decreased radioactivity in areas with patent pulmonary arteries is well established in the patients with lesions other than pulmonary thromboembolism.

Other abnormalities on lung scan not to be confused with thromboembolism include decreased radioactivity, in the apices due to pulmonary bullae, at the bases due to cardiomegaly and/or left ventricular failure, and patchy "cold areas" due to respiratory motion.

Pulmonary arteriography is specific for pulmonary thromboembolism except for microemboli and should always be performed prior to pulmonary embolectomy.—*James R. Stevenson, Captain, MC*

Ashbaugh, David G., and Petty, Thomas L. The use of corticosteroids in the treatment of respiratory failure associated with massive fat embolism. *Surg., Gynec. & Obst.*, Sept., 1966, *123*, 493–500. (From: Departments of Surgery and Medicine and the Respiratory Care Unit, University of Colorado Medical Center, Denver, Colo.)

Fat embolism may occur following a wide range of trauma. Typically, respiratory and neurologic symptoms appear 2 to 3 days after injury. It has been estimated that fat embolism carried an over-all mortality of 10 to 20 percent, and in those patients with severe cerebral and respiratory symptoms may be as high as 85 per cent.

The authors report 3 patients with fat embolism. The first patient died of acute respiratory failure. The second patient recovered from a moribund state with vigorous respiratory therapy, and in the third, respiratory failure was avoided.

The first patient received no cortisone. In the second patient, 100 mg. cortisone was given intravenously and 100 mg. cortisone acetate intramuscularly every 12 hours, when the patient entered into a moribund state. The third patient received 100 mg. cortisone intravenously 3 times a day, when the early symptoms of fat embolism appeared.

Thus, the authors conclude that the corticosteroids appeared to be a decisive factor in recovery from respiratory failure in the latter two patients. They theorize that the anti-inflammatory aspects of the corticosteroids block the chemical inflammation and pulmonary edema associated with fat embolism.

In view of their findings, they believe that further clinical trials using the corticosteroids in cases of fat embolism are indicated.—*Forrest Arnoldi, M.D.*

Fay, J. E., Fransman, S. L., Greenidge, H. W., and Power, G. R. I. Mitral insufficiency due to papillary muscle dysfunction following posterior wall infarct. *J. Canad. A. Radiologists*, Sept., 1966, *17*, 138–

141. (From: Departments of Medicine and Radiology, Queen's University and Kingston General Hospital, Kingston, Ontario, Canada.)

An apical systolic murmur indicating mitral valve insufficiency in a patient with coronary heart disease should lead one to suspect papillary muscle dysfunction secondary to myocardial infarction. Posterior wall infarction is most common. The work of Burch and co-authors is cited, in which they correlated electrocardiographic patterns with mitral insufficiency secondary to infarction of the anterolateral papillary muscle. The work of Adicoff in attempting to repair ruptured papillary muscles is also reviewed. It is recognized that patients with rupture of a papillary muscle develop congestive failure and deteriorate rapidly.

The case histories of 2 patients with coronary heart disease and papillary mitral regurgitation secondary to ischemic fibrosis of a papillary muscle are presented and illustrated with electrocardiographic and roentgenographic findings. Each of these patients had served in the Armed Forces for many years and had never had any evidence of heart murmurs prior to the development of angina pectoris.

The anatomy and physiology of the mitral valve are reviewed. The role of the papillary muscles, anterolateral and posteromedial, in proper closure of the valve is discussed.—*Richard E. Kinzer, M.D.*

Beck, Ivan T., Hernandez, Naomi A., and Solymar, Jeno, with the assistance of Phelps, E. Dyschalasia: a variant of early phase of achalasia? A review of motor disturbances in achalasia with reference to late relaxation of the lower esophageal sphincter. *Canad. M. A. J.*, Nov. 5, 1966, *95*, 941–946. (From: Department of Medicine, Sub-Department of Gastroenterology, St. Mary's Hospital, Montreal, Quebec, Canada.)

The authors investigated patients with suspected achalasia employing motility studies of the esophagus. Usually this merely confirms the diagnosis already suspected but occasionally, as in 1 case which they report, it corrected or modified the radiologic opinion.

In the normal esophagus food is propelled by peristaltic contraction proximal to the bolus and the distal esophageal sphincter relaxes before the peristaltic wave reaches it so that the bolus on arrival will meet an open channel. In achalasia the lower esophageal sphincter does not relax in a normal manner.

They report the case of a 60 year old white woman in whom a barium examination of the esophagus was initially considered to be normal, although there was a slight dilatation of the upper portion. Sixteen months later the appearance of the esophagus had changed and a diagnosis of achalasia was suggested by the radiologist. Shortly thereafter motility studies revealed all the features of achalasia except that the sphincter relaxed in response to the tertiary contractions that followed swallowing. The relaxation, however, differed from that seen in normal subjects because it was delayed. The clinical course has been good following dilatation of the sphincter.

The authors have chosen to call this condition dyschalasia. The dysphagia was due not only to lateness of sphincteric relaxation but also to the absence of normal propulsive peristaltic waves in the body of the esophagus. The question arises whether dyschalasia is a separate entity, a variety of achalasia or only an early or different state of achalasia. This cannot be answered but the authors believe that dyschalasia may be merely an early or less severe stage of achalasia.—*Arthur E. Childe, M.D.*

Buckberg, Gerald D., Dilley, Ralph B., and Longmire, William P., Jr. The protean manifestations of sclerosing fibrosis. *Surg., Gynec. & Obst.*, Oct., 1966, *123*, 729–736. (From: Department of Surgery, University of California, Los Angeles, School of Medicine, Los Angeles, Calif.)

The retroperitoneal and mediastinal spaces are continuous. Although sclerosing fibrosis occurs in both areas, only in recent years has it been pointed out that the condition has many similarities in the two areas, as regards underlying pathophysiology.

The extent of the dense fibrotic tissue varies widely in the mediastinal and retroperitoneal spaces. The symptoms are related to compression of the various tubular structures traversing these spaces. In the mediastinum, the characteristic signs and symptoms are related to superior vena caval obstruction. Obstruction and involvement of other mediastinal structures are less common, but pericardial, bronchial, esophageal and thoracic duct involvement has been recorded. Varices may occur in the upper third of the esophagus as collateral channels for superior vena caval occlusions, and these may bleed. In the retroperitoneal area the symptoms are typically related to ureteral obstruction with the characteristic colic. Intravenous urography usually reveals nonvisualization. Retrograde studies show medial deviation of the ureter with hydronephrosis. If the involvement is bilateral and severe, renal azotemia may ensue.

The etiology is unknown, although a multiplicity of causes has been suggested. A currently popular etiologic consideration is the possible relationship to hypersensitivity reactions. Histologic characteristics of the cellular aggregates in sclerosing fibrosis bear a similarity to the findings in hypersensitivity reactions.

Surgical mobilization and treatment of an involved ureter commonly are successful, although venous

bypasses have been unsuccessful in general. The course is usually selflimited and spontaneous remission may occur. Steroid therapy has been helpful in some patients.—*Mark D. Reiss, M.D.*

Abdomen

Pistocchi, G. F. Gli aspetti radiologici del volvolo gastrico. (Radiologic aspects of gastric volvulus.) *Ann. radiol. diag.*, 1966, *39*, 30–60. (From: Istituto di Radiologia, Università Degli Studi di Ferrara, Italy.)

Gastric volvulus is thought to be secondary to any congenital or acquired abnormality of the hepatoduodenal ligament in particular, or of the gastrosplenic and gastrocolic ligaments. Not infrequently a gastric volvulus is associated with esophageal hiatus hernia, relaxation or eventration of the diaphragm.

In complete or true volvulus the rotation of the stomach is of more than 180° along one of its major axes. In partial or segmental gastric volvulus only one segment, usually the pyloric, is involved.

In the most common form, the *organo-axial*, the stomach rotates along its longitudinal or coronal axis. Two types are described: an infracolic and a supracolic. In most of the cases the position of the colon remains unchanged, below the level of the rotated stomach (supracolic type).

In *mesentero-axial* rotation the stomach rotates along the axis of the gastrohepatic ligament, either from right to left or from left to right.

In exceptional cases of severe *gastroptosis* with marked atony of the stomach, the rotation may occur along the sagittal or anteroposterior diameter of the stomach.

Gastric volvulus is often intermittent, may disappear completely or become chronic. It is only the acute gastric volvulus which constitutes a surgical emergency.

The most common roentgen findings in gastric volvulus are: massive and localized distention of the stomach or of a segment; frequent demonstration of the so-called inverted alfa sign, produced by an incisura along the superior contour of the stomach and opened toward the right hypochondrium or dorsally; and unchanged appearance of the stomach regardless of the position assumed by the patient.—*A. F. Govoni, M.D.*

Jacquemet, P., Mestrallet, G., Jouvinroux, P., and Maillet, P. (Lyon, France.) Valeur diagnostique des signes radiologiques dans les sténoses hypertrophiques du pylore de l'adulte. (The diagnostic value of radiologic signs in hypertrophic stenoses of the adult pylorus.) *J. de radiol., d'électrol. et de méd. nucléaire*, Oct., 1966, *47*, 489–496.

Hypertrophic stenosis in the adult is usually an acquired lesion; it is most often associated with inflammatory disease, although it is not known why certain ulcers provoke such a reaction and others do not.

There are two types, depending on whether the pylorus only is involved, or whether there is proximal extension into the antrum.

In the simpler type there is usually an hour-glass or annular narrowing, usually symmetric; the canal is regular, with the hypertrophic tissue at times making a curvilinear imprint on the bulb, or thrusting into it in a pattern which resembles the uterine cervix. If, however, the antrum is involved, the pattern is more varied; the canal is lengthened and resembles the finger of a glove, or if the lesion is several centimeters long it may either be cylindrical or conical (in the latter case it resembles a malignant infiltrate). The stomach proximal to the lesion may be dilated. If the mucous membrane folds are parallel there is a presumption that the lesion is benign. Prepyloric spurs may be seen on one or both curvatures, and a groove may separate normal from hypertrophic tissue. Ulcers may be present, as they were in 3 of the authors' 5 cases; they may be recent and supple or callous and cicatricial. The most difficult types of hypertrophic stenoses to evaluate are those having myomatous nodules, anarchic distribution of mucous folds and those in which the stenosis is complete.—*Frank A. Riebel, M.D.*

du Plessis, D. J. Primary hypertrophic pyloric stenosis in the adult. *Brit. J. Surg.*, June, 1966, *53*, 485–492. (From: Department of Surgery, University of the Witwatersrand and the Johannesburg General Hospital, Johannesburg, Union of South Africa.)

Hypertrophic pyloric stenosis is not a rare disease in adults. Recent reports indicate that it accounts for between 2 to 3.5 per cent of all cases of pyloric obstructions in adults. It may be a persistence of the infantile variety, or secondary to some other upper gastrointestinal lesion, or a primary lesion.

The main symptom of primary hypertrophic pyloric stenosis is upper abdominal discomfort after meals, relieved by vomiting, but not by antacids. No physical signs except possibly a distended stomach is present.

The radiologic picture is an elongated, narrowed pyloric canal which may have an upward curve, and near its mid point on the greater curvature a crevice may be seen. If the hypertrophy is severe there may be an indentation in the base of the duodenal bulb. Delay in gastric emptying is the usual rule.

The author presents his experience with 6 cases of primary hypertrophic pyloric stenosis.

He concludes that in the primary variety there is a deficiency in the longitudinal layer of the muscle along the pyloric canal, probably on a congenital basis. He suggests that this leads to ineffectual emptying contractions of the pyloric canal, resulting in a

functional obstruction and later work hypertrophy of the circular muscle, which will add a mechanical component to the obstruction. Proximal to the pyloric canal there is hypertrophy of the longitudinal and circular muscle layers of the stomach.

Gastritis, gastric ulcerations, or even mucosal structures in the pyloric canal may occur secondarily to the obstruction.

In view of the fact that the obstruction at the pylorus is partly functional, the author advises partial gastrectomy instead of more conservative operations. —*Forrest Arnoldi, M.D.*

Louw, J. H. Abdominal complications of Ascaris lumbricoides infestation in children. *Brit. J. Surg.*, June, 1966, *53*, 510–521. (From: Department of Surgery, University of Cape Town, South Africa.)

The author reports on 100 cases of acute abdominal emergencies secondary to Ascaris lumbricoides infestation in children. Ascaris infestation is still quite prevalent in Africa and the Far East. In Cape Town approximately 70 per cent of the Negro children are infested after the age of 1 year. The 100 cases accounted for 12.8 per cent of acute abdominal emergencies in the age period newborn through 12 years. Abdominal emergencies secondary to ascariasis ranked second only to appendicitis. Of deaths from 731 consecutive abdominal emergencies in children, 37.5 per cent were secondary to ascariasis.

The diagnosis was based on the presence of worms in the vomitus or stools, abdominal masses and positive roentgenographic findings. Plain roentgenograms of the abdomen in 16 cases revealed not only evidence of intestinal obstruction but also the presence of worms in the bowel manifested by wisp-like radiolucent lines in a somewhat parallel manner.

Conservative therapy is recommended but laparotomy should be performed in the following circumstances: (1) the passage of blood per rectum; (2) a very ill child with tense abdominal distention and rebound tenderness; (3) the presence of multiple fluid levels on abdominal roentgenograms; and (4) unsatisfactory response to conservative therapy.

When primary peritonitis occurred in association with ascariasis in a severely malnourished child it was extremely lethal. Generally, however, appendicitis and primary peritonitis were uncommon.

Biliary obstruction was surprisingly frequent. When suspected, the diagnosis of biliary ascariasis was confirmed by roentgenographic investigation or laparotomy. Particularly useful were the intravenous cholangiography and tomography. The intravenous cholangiogram with tomography may show a filling defect in the common duct caused by the round worm. Sometimes the only finding on cholangiography may be dilatation of the biliary tree with no intraluminal obstruction. The presence of worms in the duodenum is considered strong presumptive evidence of biliary ascariasis and it may even be possible to demonstrate ascent of Ascaris into the common duct. In biliary ascariasis conservative treatment is recommended for uncomplicated cases but laparotomy is suggested in the following circumstances: (1) marked jaundice (serum bilirubin above 3 mg. per cent); (2) gross irregular hepatic enlargement; (3) associated local or generalized peritonitis; and (4) persistence of a shadow in the common duct on intravenous cholangiography.

Pancreatitis due to Ascaris was also more common than is generally appreciated. In addition to the presence of worms in the vomitus or stools, severe upper abdominal pain and tenderness, raised serum amylase and a palpable pseudocyst were often present. This was corroborated by roentgenograms of the abdomen which showed an enlarged mass in the pancreatic region displacing the colon. In at least one case there was also associated pancreatic calcification demonstrated by roentgenography. Twenty-five per cent of cases with pancreatic ascariasis also had associated biliary obstruction. Again conservative treatment is advised in acute pancreatic ascariasis but laparotomy should be performed: (1) if there is doubt about the diagnosis; (2) in the presence of very large or expanding pseudocysts or formation of chronic granulomata with biliary obstruction; and (3) with failure of response to conservative measures.—*Lionel W. Young, M.D.*

Sheiner, N. M., Palayew, M. J., and Sedlezky, I. Gas in the portal vein: a report of two cases. *Canad. M. A. J.*, Sept. 17, 1966, *95*, 611–615. (From: Departments of Surgery and Radiology, Jewish General Hospital, Montreal, Quebec, Canada.)

Gas in the portal vein is an ominous sign which is detectable on plain roentgenograms.

Two cases with gas in the portal vein are reported and discussed. Both patients had extensive intestinal necrosis, due in one case to a volvulus of the small intestine around a mesenteric band and in the other to occlusion of the superior and inferior mesenteric arteries and celiac axis. Both patients died.

The literature on this subject is reviewed and a distinction is made between portal vein gas and biliary tree gas. The possible sources of portal gas are presented and the clinical significance of this entity in infants and adults is discussed.—*John H. Harris, M.D.*

Pons, H., Madray, Mme., and Seifer, A. Étude de l'évacuation des voies biliaires basée sur 200 cholécystographies (comparaison des résultats fournis par le repas gras dosé et une nouvelle association: sorbitol-cyclobutyrol sodique et sulfate d'atropine, en tant que repas de Boyden). (A study concerning the emptying of the biliary pathways

based on 200 cholecystographies [comparison between the results obtained with the proportionated fatty meal and with a new mixture: sorbitol-sodium cyclobutyrol and atropine sulfate given in place of Boyden's meal].) *J. de radiol., d'électrol. et de méd. nucléaire*, Oct., 1966, *47*, 497–506. (From: Service de Radiologie centrale du Centre Hospitalier Universitaire de Toulouse, France.)

A substitute for the fatty meal used during cholecystographies has been developed which contains sorbitol-sodium cyclobutyrol and atropine sulfate (S.C.A.). One hundred cases were studied using this mixture and compared to 100 cases wherein the standard fatty meal was used; the results were essentially equal.

S.C.A. is proposed for those cases in which the use of fats is contraindicated or unpalatable; it is of further advantage when it is desired to follow with a gastrointestinal examination since it is aqueous, highly fluid and occupies only 10 cc.—*Frank A. Riebel, M.D.*

Glenn, Frank, and Whitsell, John C., II. Primary sclerosing cholangitis. *Surg., Gynec. & Obst.*, Nov., 1966, *123*, 1037–1046. (From: Department of Surgery, The New York Hospital-Cornell Medical Center, New York, N. Y.)

The authors state that this is an uncommon disease of unknown causation which presents perplexing problems from the point of view of both diagnosis and therapy. They have studied 7 patients with this condition, none of whom have been exposed to previous surgical injury to the bile ducts or any portion of the biliary tract. The gallbladder in each patient exhibited some degree of fibrosis but calculi were present in only 3. Enlargement of lymph nodes along the common duct was frequently accompanied by edema and fibrosis in the region of Calot's triangle. The external diameter of the common duct although not increased and even sometimes reduced was firm and thickened to palpation in each patient. Narrowing of various portions of the biliary tree was demonstrated by operative cholangiography in 6 of the 7 patients. This procedure could not be performed in the 7th patient because of almost complete obliteration of the lumen of the common duct. Biopsies of the common duct were done in 4 patients and dense avascular fibrous tissue was demonstrated in 3. There was no evidence of carcinoma of the biliary tract in any of these cases.

Definite diagnosis of this lesion can only be made by exploratory celiotomy. Operative cholangiography is useful in determining the extent of the disease and biopsy of the common duct is essential. The clinical course is variable but the majority of these patients have an ultimate unfavorable prognosis due to the development of biliary cirrhosis.—*Arthur E. Childe, M.D.*

Gynecology and Obstetrics

Barabas, A. P. Ehlers-Danlos syndrome: associated with prematurity and premature rupture of foetal membranes; possible increase in incidence. *Brit. M. J.*, Sept. 17, 1966, *2*, 682–684. (Address: Surgical Registrar, the Postgraduate Medical School of London, and Hammersmith Hospital, London, England.)

The Ehlers-Danlos syndrome is an inherited disorder of the connective tissue. It belongs to the same group of disorders as the Marfan syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. The main clinical features are: fragility of the skin and of the dermal blood vessels, characteristic "papyraceous" scars, hyperextensible skin and hypermobile joints.

The author presents evidence that most babies with Ehlers-Danlos syndrome are born after premature rupture of fetal membranes. In all patients the fragility of fetal membranes (as shown by the degree by prematurity) is well correlated with the fragility of skin (as shown by the amount of skin scarring). It is argued that in countries with good antenatal and premature infant care an increase in the number of surviving Ehlers-Danlos syndrome patients is likely.

Eighteen patients with Ehlers-Danlos syndrome were studied. Fourteen patients (78 per cent) were born prematurely, owing to premature rupture of the fetal membranes. Most of the non-premature births occurred in one large exceptional family.—*Eugene J. McDonald, M.D.*

Nichols, John, and Schrepfer, Rosemary. Polyhydramnios in anencephaly. *J.A.M.A.*, Aug. 15, 1966, *197*, 549–551. (Address: Dr. Nichols, University of Kansas Medical Center, Rainbow Boulevard and 39th Street, Kansas City, Kan. 66103.)

Four cases are presented which challenge the common etiologic concept of polyhydramnios resulting from "failure to swallow."

One newborn with esophageal atresia of 9 cm. showed a normal amniotic fluid volume. A second had a 1 cm. esophageal atresia but showed radiologic evidence of sodium diatrizoate in the bowel after amniocentesis and 30.0 cc. contrast medium replacement. Two other cases of anencephaly are presented in which the infants swallowed the radiopaque media, and yet both mothers had hydramnios.

The authors quote 3 cases of Jeffcoate and Scott (1959) which are exactly the opposite.

The origin, circulation, function and resorption of amniotic fluid are complex. The well recognized in-

creased incidence of polyhydramnios in cases of anencephaly and stenosis and atresia of the alimentary tract is usually attributed to "failure of the fetus to swallow." This article emphasizes that this phenomenon is still not fully understood.—*Eugene J. McDonald, M.D.*

Spencer, Richard P., Fishbone, Gerald, and Davis, Clarence D. Amniotic fluid studies by isotope dilution and scanning. *J. Nuclear Med.*, Aug., 1966, *7*, 629–632. (From: Departments of Radiology and Obstetrics & Gynecology, Yale University School of Medicine, New Haven, Conn.)

Two women in the fourth month of gestation were studied just before induction of therapeutic abortion. Fifty microcuries of I^{131} human serum albumin were introduced by amniocentesis. Scannings were performed 1 hour later.

Within the first 24 hours after injection, only small amounts of radioactivity had left the amniotic fluid space. There was less than 1 per cent bound to the fetus, as determined by counting after delivery. Later studies will be performed with only 10 or 20 microcuries. If delivery occurs within a few hours after the radioalbumin is introduced, radiation doses to the fetus will not be excessive.

Possible uses of the procedure are in estimating amniotic fluid volume, its distribution, placental localization, and fetal position after engagement. Because of absorption of most of the radiation in the fluid, scanning from several positions may be necessary for precise determination of the fetal position.—*Eugene J. McDonald, M.D.*

Blood and Lymph System

Love, Robert W., Jr., and Takaro, Timothy. Lymphangiography with direct roentgenographic magnification: new application for an old technic. *Radiology*, July, 1966, *87*, 123–127. (From: Veterans Administration Hospital, Oteen, N. C.)

Lymphangiograms were obtained in 25 patients by both conventional techniques and direct roentgenographic magnification and the results were compared. After administration of the ethiodol, conventional roentgenograms of the pelvic area, the abdomen, and the chest were taken. The patient was then elevated 18 to 20 inches above the table top and magnified images, twice normal size, were obtained of each inguinal area, of the pelvic lymph nodes, and of the abdominal lymph nodes, while the lymphatic channels were still opacified. The following day, these studies were repeated.

In the 25 patients studied, the diagnoses were lymphoma in 7, carcinoma of a pelvic organ in 7, malignant melanoma, hemochromatosis, sarcoidosis, and nonspecific reactive hyperplasia in 1 each. No pathologic condition was noted in 5 patients.

It was found that the magnified roentgenograms showed increased detail in morphology of the fine lymphatic channels and the lymph nodes in 21 instances. Besides enhancing detail, the magnification technique may allow the recognition of small changes in the size and structure of lymph nodes following irradiation or chemotherapy.—*A. W. Sommer, M.D.*

General

Ettinger, Alice, and Fainsinger, Maurice H. Zonography in daily radiological practice. *Radiology*, July, 1966, *87*, 82–86. (From: Department of Radiology, Tufts-New England Medical Center, New England Center Hospital, Boston, Mass.)

Zonography is a variation of tomography in which body section studies are obtained using a small angle of tube arc. In tomography where wide angles of tube movement are used excellent blurring of structures close to or remote from the plane of interest are achieved. In zonography blurring of structures remote from the plane of interest are also obtained, but blurring of structures close to the plane of interest is incomplete. This results in a relatively thicker layer which is in focus with the zonograms closely resembling a conventional roentgenogram permitting much easier orientation and interpretation than in tomography. Detail and contrast have also been found to be superior. Zonograms may be obtained with use of pluridirectional movement or linear movement.

The authors, using a linear movement apparatus which has been modified to allow a 5° angle technique, report their assessment of the usefulness of zonography in clinical practice. Zonograms obtained during the early stages of intravenous urography, usually at 3 minutes, permit visualization of the renal contour in nearly all cases irrespective of gas and fecal shadows which are adequately blurred. In some cases of renal cysts, the differential density between the avascular cyst and the vascular parenchyma has been obvious particularly when a dose equal to at least 50 cc. of hypaque 50 is used. The collecting system has been demonstrated to good advantage in patients with much overlying bowel gas and, in addition, the sharpness of the calyces is quite superior to that obtained with tomography.

The authors feel that the most rewarding application of the zonographic technique is during intravenous cholangiography where often 1, and at the most 3, zonographic cuts will show the entire common hepatic and common bile ducts, including the drainage of contrast medium into the duodenum. In studies on the lungs and bronchi, linear zonography has permitted visualization of the major bronchi down to the segmental level and has been found useful in attempting to differentiate between inflamma-

tory disease and malignancy. In a survey of the lungs for obscure multiple metastases, the entire lung fields can be examined in 4 or 5 sections. In studies of the skeletal system, this technique has been found superior to conventional roentgenograms in examination of the flat bones such as the sternum and sacrum. The lateral projections of the upper dorsal vertebrae, the lateral mandible, and the temporomandibular joints can also be studied adequately, and in cases of trauma where positioning of the patient is difficult, detailed information may be obtained rapidly without moving the patient as for multiple conventional projections.

The authors conclude that zonography lends itself to frequent application in daily practice because of its simplicity and efficiency.—*Donald N. Dysart, M.D.*

Lotz, K., Reichel, W. S., and Tautz, M. Grundlagen der Mammographie. (Fundamentals of mammography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1966, *105*, 229–239. (Address: Städtisches Klinikum Berlin-Buch, Radiolog. Klinik, Wiltbergstrasse 50, X 1115 Berlin-Buch, Germany.)

Roentgenograms of satisfactory definition and contrast can be obtained with a high tension apparatus operating in a range between 25–35 kv. All added filters are removed in order to bring the remaining filtration below 2.0 mm. Al. No substantial difference in quality could be seen between filtrations of 0.6–1.6 mm. Al. The authors prefer a focal-film distance of 40 cm. since such distances as 50–80 cm. only increase the exposure times. Supervidox film (VEB Chemische Werke, Berlin) is non-screen and is equivalent to Radiolix (Gevaert), Perlutz Type S, and Adox.

A single intensifying screen above the non-screen film permits a reduction in mas., improves contrast, increases the photographic effect and reduces the dose to the patient. The skin dose is less than 1 r per exposure; the gonadal dose is less than 1.0 mr per exposure.—*J. Zausner, M.D.*

McIlvanie, Samuel K. Wegener's granulomatosis: successful treatment with chlorambucil. *J.A.M.A.*, July 11, 1966, *197*, 90–92. (From: Hematology Section, Department of Medicine, Rockwood Clinic, Spokane, Wash.)

The author reports regression of all lesions and relief of symptoms in 2 patients with Wegener's granulomatosis using prolonged courses of chlorambucil. One patient was clinically well 22 months and the other 12 months following the therapy. A reversal of abnormal protein electrophoretic pattern was demonstrated in both patients.

He feels that failure to control this disease with chlorambucil, as reported by others, may be attributed to inadequate trial; and he believes that the success of the treatment in his cases was due to higher doses and longer treatment times.

While the report is limited to 2 cases and the control times are relatively short, the result is encouraging and the treatment of Wegener's granulomatosis with prolonged doses of chlorambucil certainly warrants further clinical trial.

The reader is referred to the original article for recommended dosages.—*Ned B. Hornback, M.D.*

Chang, M. C., Hunt, Dorothy M., and Turbyfill, C. L. Fertilization and early development after radiocobalt irradiation of rabbit oocytes and sperm in the female tract. *Anat. Rec.*, April, 1966, *154*, 713–726. (From: Worchester Foundation for Experimental Biology, Shrewsbury, Mass.)

This paper is a report of the investigation of the effect of ionizing radiation on rabbit sperm, oocytes, and fetal development. Radioactive cobalt was used. With simultaneous irradiation of ovarian oocytes and sperm in the female tract, it was found that neither rate of ovulation nor fertilization was affected; however, cleavage of the fertilized ova was retarded, and the transportation of ova was disturbed. Fertilized ova failed to develop, and embryonic development failed as no fetuses or decidual tissue were found when 10 females were examined 27 days later.

When oocytes alone were irradiated after an ovulating injection, the fertilization rate was lower. Only one small blastocyst, probably incapable of implantation, was recovered when examined 6 hours after mating. This shows that the oocytes were more sensitive to irradiation than were the fertilized ova.

In another group of rabbits, sperm was recovered from the vagina and uterine horns of female rabbits soon after irradiation, and was inseminated into rabbits which had received an ovulating injection 4 to 8 hours previously but had received no irradiation. About 30 per cent of the fertilized ova developed into normal blastocysts and 20 per cent developed into apparently normal fetuses, indicating that irradiation of sperm in the female tract was much less harmful than irradiation of oocytes.

A detailed discussion of the experiments, together with charts and reproductions of illustrative plates, is presented.—*Douglas S. Kellogg, M.D.*

RADIATION THERAPY

Morrison, Robert, and Deeley, Thomas J. The treatment of recurrent carcinoma of the bladder by supervoltage radiotherapy. *Brit. J. Urol.*, June, 1966, *38*, 319–322. (From: Radiotherapy Department, Hammersmith Hospital, London, W.12, England.)

The authors report their results of treatment by

supervoltage radiation technique of 97 patients with various types of carcinoma of the bladder where the tumor was known to have recurred following surgery or where pathologic report on the excised tissue suggested that recurrence was inevitable. The histologic distribution was similar to that of a group of untreated cases. The technique employed was similar to that used for treatment of previously unoperated cases; *i.e.* the whole pelvis was irradiated and the fields extended to include the operative scar. A tumor dose of 4,500 rads was planned to be given in 1 month.

Of the 97 cases, 43 (48 per cent) represented cases in which operation was incomplete and had a 5 year survival of 28 per cent, while the remainder of 47 cases (52 per cent) represented patients with recurrent tumor and had a 5 year survival of 29 per cent following radiotherapy.

A comparison is made of 55 patients with transitional cell carcinoma treated by radiotherapy following surgery, who had a 4 year survival of 36 per cent, with 82 cases of T_1 and T_2 transitional cell tumors treated by radiotherapy only, who had a 4 year survival of 39 per cent to show that there is no statistical difference and that postoperative radiotherapy is worthwhile.

Early and late complications are enumerated and show no statistical difference in incidence when compared to patients having had no previous surgery.—*John Truksa, M.D.*

RADIOISOTOPES

Nofal, Mohammed M., Beierwaltes, William H., and Patno, Mary Ellen. Treatment of hyperthyroidism with sodium iodine I^{131}: a 16-year experience. *J.A.M.A.*, Aug. 22, 1966, *197*, 605–610. (From: Departments of Internal Medicine and Biostatistics, University of Michigan, Ann Arbor, Mich.)

This is a report of the follow-up study of the incidence of hypothyroidism among 848 patients treated with radioactive iodine (I^{131}) for hyperthyroidism, as compared with 121 patients treated surgically for hyperthyroidism. The diagnosis of hypothyroidism was made on the basis of three criteria: (1) symptoms and signs raising the possibility of hypothyroidism; (2) at least one confirmatory laboratory test, usually a serum PBI value of less than 3.5; (3) a confirmatory clinical response to thyroid medication.

The authors state that there seems little doubt that with relief of thyrotoxicosis by either I^{131} or surgery, the incidence of hypothyroidism increases rapidly soon after treatment, and then continues at a rate of 1 per cent to 3 per cent therafter. Their study shows that after treatment with I^{131} the cumulative percentage of hypothyroidism increases 5.5 per cent per month during the first 6 months, 1.3 per cent per month during the second 6-month period, and thereafter 2.8 per cent per year. Data on the surgically treated patients produced a similar curve, but with smaller increments: 3.7 per cent per month during the first 6 months after surgery, 0.51 per cent per month in the second 6-month period, and thereafter 1.7 per cent per year.

If the cumulative incidence curves of hypothyroidism were to continue as they have during the first 10 years after treatment with I^{131} or surgery, almost everyone treated with either method should face the eventual possibility of developing hypothyroidism. No definite morbidity or mortality has been established for treatment with I^{131} as contrasted with the well established inconvenience, morbidity, and mortality following surgery.—*Douglas S. Kellogg, M.D.*

Baum, Sheldon, Silver, Lawrence, and Vouchides, Despina. The recognition of hepatic metastases through radioisotope color scanning. *J.A.M.A.*, Aug. 29, 1966, *197*, 675–679. (Address: Department of Nuclear Medicine, Long Island Jewish Hospital, Queens Hospital Center Affiliation, Jamaica, N. Y.)

The authors undertook to test the accuracy of color-printed radioisotope scintigrams of the liver in a group of 116 patients in whom a hepatic diagnosis was proved by biopsy, operation, or postmortem examination. A tracer dose of 150 μc of colloidal Au^{198} was always employed, and scans were done on one or the other of two scanners, one equipped with a 3 inch crystal detector, and the other with a 5 inch crystal. Each of the scanners was fitted with a color print-out system in which the full range of counting rate in the volume of interest was displayed in a 10 color spectrum. Scans were interpreted as being positive for space-occupying lesions in 46 patients, of whom 41 were proved to have metastases, an accuracy rate of 89 per cent. This value is comparable to that reported in several other series. In the remaining 70 patients the scan was interpreted as negative for evidence of space-occupying disease, and the diagnosis was found to be correct in 69 instances. An accuracy rate of 98 per cent for negative scans is higher than is usually encountered.

The authors believe that color renditions of scan data make it possible more easily to detect semiquantitative differences in counting rates, making it easier to discriminate small lesions.

It is interesting to note the level of accuracy to which hepatic scanning can be brought in a highly selected patient group.—*Frederick J. Bonte, M.D.*

Harris, C. C., Satterfield, M. M., Uchiyama, Guio, and Kimble, Harry E. A rescanner with photographic color readout. *J. Nuclear Med.*, July, 1966, *7*, 501–509.

(From: Oak Ridge National Laboratory, and Oak Ridge Associated Universities, Oak Ridge, Tenn.)

In the past the authors have developed a device known as a "rescanner," a system used to process further the information contained in original photoscans. They describe this instrument as an analogue computer, capable of integrating recorded information over a definite area.

They have further adapted this apparatus with a photographic color attachment consisting of a light source, a rotating color wheel, and a Polaroid color camera. The entire system is shown in block diagram form. The various segments of the color range represent different counting rate levels.

A number of color scan records made with this interesting device are shown.—*Frederick J. Bonte, M.D.*

KUHL, DAVID E., HALE, JOHN, and EATON, WALTER L. Transmission scanning: a useful adjunct to conventional emission scanning for accurately keying isotope deposition to radiographic anatomy. *Radiology*, Aug., 1966, *87*, 278–284. (From: Department of Radiology, School of Medicine and Hospital of University of Pennsylvania, and the William H. Donner Center for Radiology, Philadelphia, Pa.)

The transmission scan and its uses are discussed. The authors point out the difference between the usual scan which is obtained when an organ concentrates an isotope whose emissions are recorded by a scintillation detector (the emission scan) and the transmission scan. The latter is obtained by recording impulses passing from a low-energy external photon source on one side through the patient to a scintillation detector on the opposite side of the body. Such a scan will produce an image due to differential photon absorption by body tissues, much like the conventional roentgenogram.

The authors feel that the primary use of the transmission scan is its ability to aid in orientation of primary organ (emission) scans to the surrounding body structures—a task which heretofore has been accomplished with only fair success by correlation of scan "landmarks" with roentgenograms, due to distortion and patient movement.

The transmission scan is obtained simultaneously with the emission scan by yoking a radioactive source in a collimator to the detector, but in a fashion where the source and detector are positioned facing each other on opposite sides of the patient's body, and moving in a fixed relationship. The detector thus will receive impulses from the primary organ being scanned, as well as impulses transmitted through the body from the source. A pulse-height analyzer separates the emitted and transmitted impulses, which are recorded on two separate scans.

The sources most often used by the authors are americium 241 or iodine 125, both low-energy photon emitters. Collimation in the source shield and in the detector allows only the small cylinder of tissue between the 2 apertures to be scanned at any instant.

The transmission and emission scans can be directly superimposed. Any patient movement will be evident on both scans, and the effects of distortion are eliminated. The authors also describe the use of opposing detectors, with the photon source mounted in one detector head, for simultaneous bilateral or anterior and posterior emission scans together with a transmission scan.

Clinical uses are considered, the most promising ones being: (1) comparison of the cardiac outline and blood pool in scans for pericardial effusions; (2) correlation of the liver dome with the diaphragm in liver scans for subphrenic abscess and to eliminate respiratory motion "liver scalloping" artefacts; (3) correlation of pulmonary lobar anatomy with emission mapping of regional pulmonary artery perfusion; and (4) relating transverse-section emission scans to cross-sectional body anatomy, particularly in the mediastinum.—*James A. Cunyus, M.D.*

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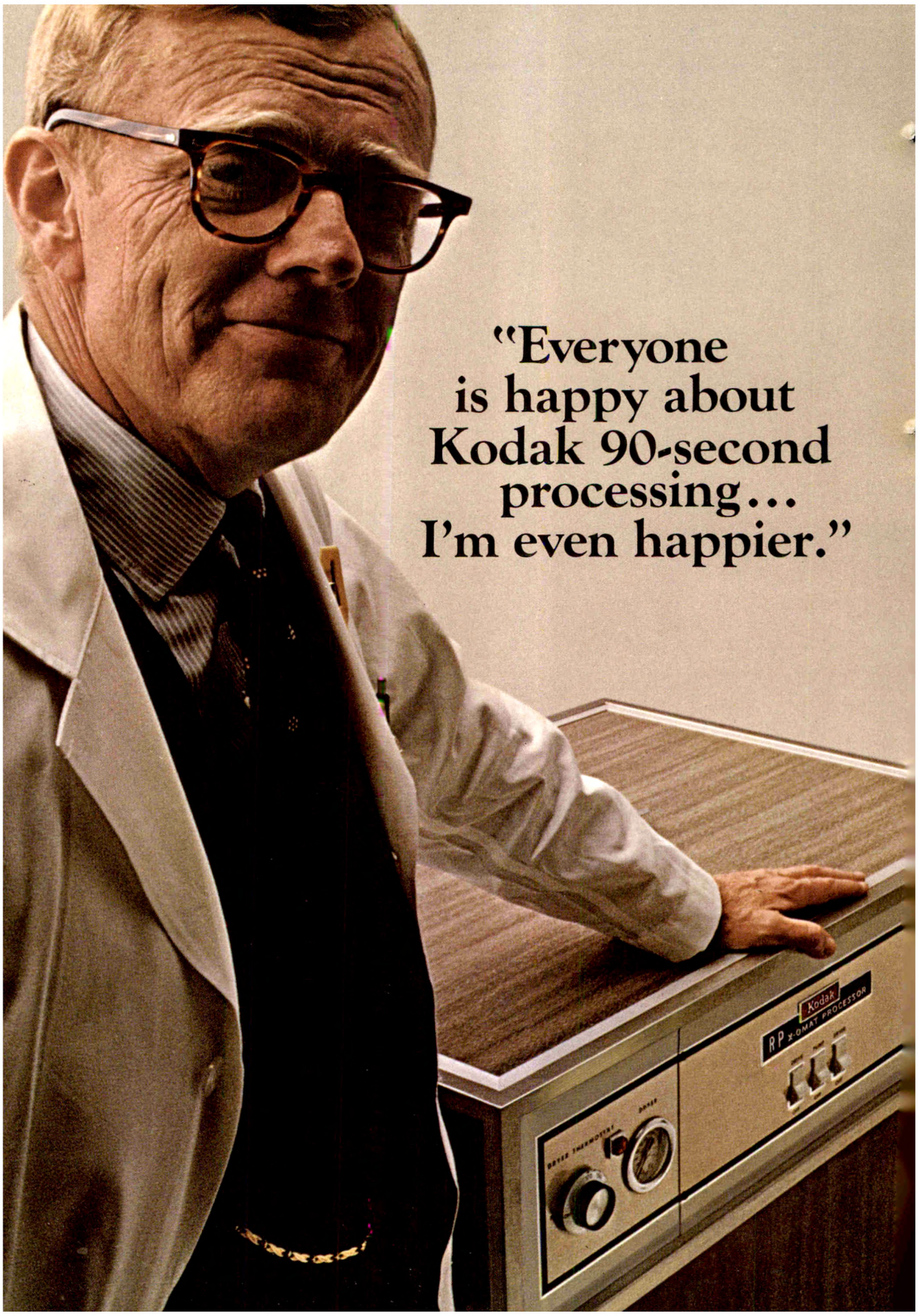
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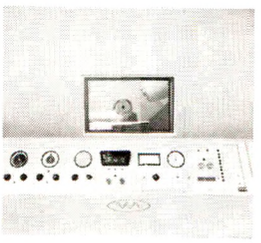
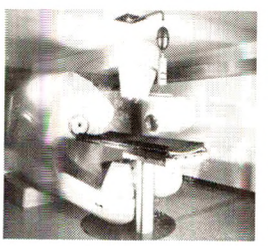
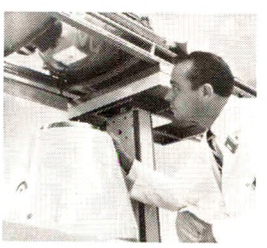
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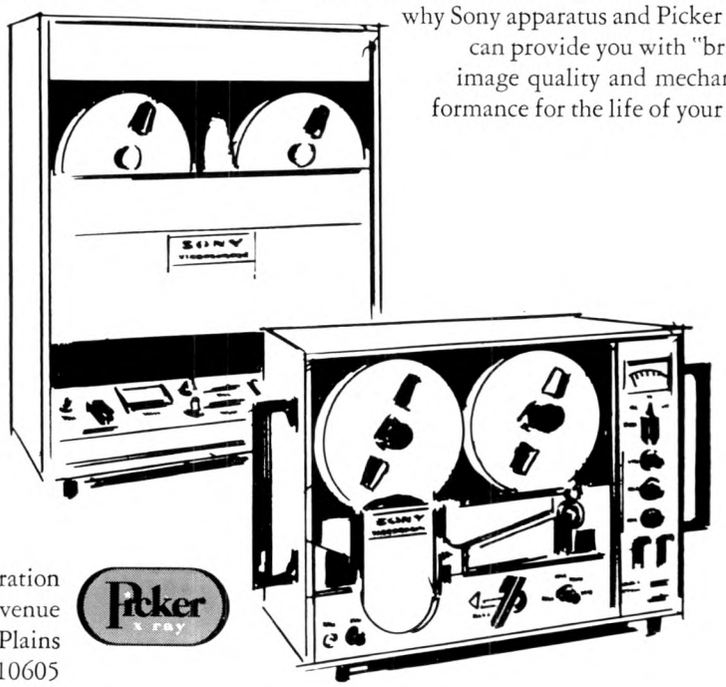
One reason why Sony videorecorders stand out is their use of the exclusive "Rotocoil" frictionless recording and play-back head. Rotocoil heads stay clean and require very little maintenance in order to preserve the high fidelity performance of a brand new machine. The degradation of image quality that is almost taken for granted with other video tape recorders that need constant cleaning is avoided by the Rotocoil principle.

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Sony videorecorders have proven their consistent quality and reliability in hundreds of radiological installations, installed and serviced by Picker. The consistent high fidelity of images preserved on Sony magnetic tape has been demonstrated by countless and repeated play-backs. Even when subjected to the rigors of stop-motion displays.

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same day re-examination in oral cholecystography

obviously practical, but... diagnostically valuable?

UNSATISFACTORY opacification after routine cholecystography doesn't necessarily mean the gallbladder is diseased. Poor absorption of the contrast agent from the gastrointestinal tract, or the inability of the liver to conjugate and excrete it, might just as well be the cause.[1]

'Nonopacification' is not a condition you can treat

To determine the cause of nonopacification, most physicians request re-examination. There are two ways this has been done by the oral route in the past:

- by starting all over again at a later date — and sometimes doubling the dose of contrast agent on the second try;
- by administering more contrast agent the evening of the first unsuccessful examination (and, again, sometimes doubling the dose) and repeating the study the following day.

Both these methods share two inherent disadvantages. They take a good deal of time, and they require the patient to take a good deal of oral contrast agent. The amount given assumes clinical importance because it has been reported higher doses may result in considerable patient discomfort because of diarrhea and other significant side effects.[1]

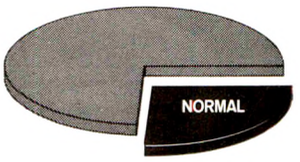
Recently it's been demonstrated, however, that the use of Oragrafin Calcium (Squibb Calcium Ipodate) permits repeat films with significant cuts in both time and total dosage.

Oragrafin Calcium—absorbed so rapidly you can re-examine the same day

"The advantage of the calcium ipodate method is that the examination can be completed in five additional hours with a limited dose of contrast agent."[1]

The method is as productive as it is simple. If the initial opacification is unsatisfactory, the patient is given 3 Gm. of calcium ipodate. Films are repeated 5 hours later. Here ar the results of a recently published study on same day re examination using Oragrafin Calcium:[1]

ANALYSIS OF ORAGRAFIN CALCIUM REENFORCEMENT
IN 76 CASES OF UNSATISFACTORY INITIAL OPACIFICATION



Positive information 24 { Normal by present criteria 20; Cholelithiasis 4
Abnormal gallbladder (by inference) 52

Correlation of x-ray findings and surgical data was excellent. Because many patients were elderly or had complications contraindicating it, surgery was performed in only 13 cases, with these results: Stone — 6; Liver metastases — 3; Carcinoma of pancreas — 1; Carcinoma of gallbladder — 1; Cirrhosis — 1; Normal — 1

Had the initial failure of opacification been assumed to b due to gallbladder disease, the 20 patients (26%) foun normal by re-examination might have been erroneousl diagnosed and might have undergone unnecessary surgery.

"Same day re-enforcement oral cholecystography utilizin calcium ipodate . . . is a rapid, accurate, low-dose method o obtaining additional information about a gallbladder whicl is unsatisfactorily opacified following routine cholecystog raphy."[1]

There are other advantages to such rapid absorption. Ever without prior preparation of the patient, both cholangiog raphy and cholecystography can be performed on the sam day. Optimal concentration in the hepatic and biliary duct usually occurs within 1 to 3 hours. Although the gallbladde is optimally opacified approximately 10 hours after ingestion of Oragrafin, diagnostically valuable information can ofter be obtained within 5 hours or less.

Dosage and Administration: For oral combined cholangiography an cholecystography: *Same day* — Oragrafin Calcium Granules — 2 packet 1 hour before initiating examination. *Overnight* — Oragrafin Calcium Granules—1 packet or Oragrafin Sodium Capsules (Squibb Sodium Ipodate) — 6 capsules 10 to 12 hours before radiography, plus an additiona packet of Granules one hour before examination.

Supply: Oragrafin Calcium Granules — single-dose foil packets of 3 Gm of calcium ipodate granules, providing 61.7% iodine content. Oragrafi Sodium Capsules — 0.5 Gm. sodium ipodate per capsule, providing 61.4% iodine content.

Contraindications: Contraindicated for persons sensitive to oral iodin compounds or for patients with combined renal and hepatic disease o severe kidney impairment. Gastrointestinal disorders (which may resul in inadequate biliary secretion of medium) often impair visualization.

Side Effects and Precautions: Both calcium and sodium ipodate ar usually well tolerated. Mild and transient nausea, vomiting, or diarrhe sometimes occur; but the incidence can be reduced by using the calciur Granules and restricting the dosage to 3 Gm.

Hypersensitivity reactions may include urticaria, serum sickness-lik reactions (fever, rash, arthralgia), other skin reactions, and rarely ana phylactoid shock. They are more likely to occur in the individual with hypersensitivity diathesis. Antihistamines and corticosteroids are used t control these side effects, but the occasional serious anaphylactoid reaction require the immediate use of epinephrine or phenylephrine, oxygen, an intravenous corticosteroids. For full information see Package Insert.

Reference: 1. Crummy, A. B.: Wisconsin M. J.: 65:84, 1966.

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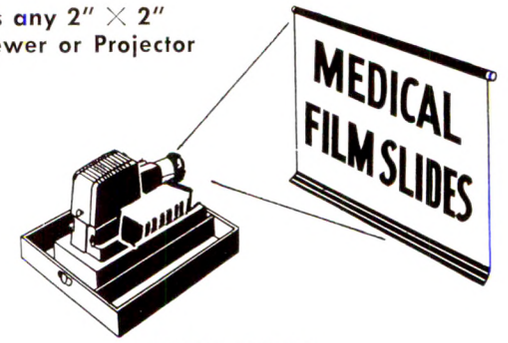
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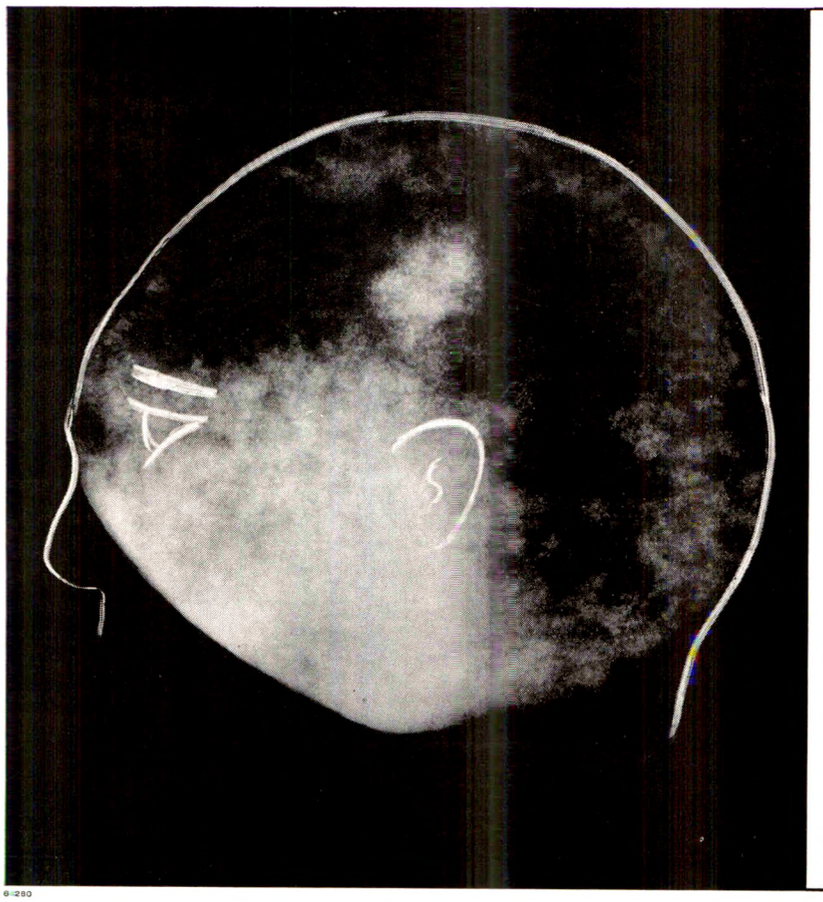
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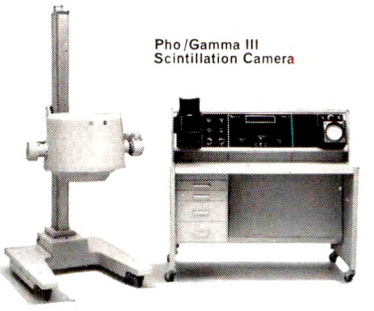
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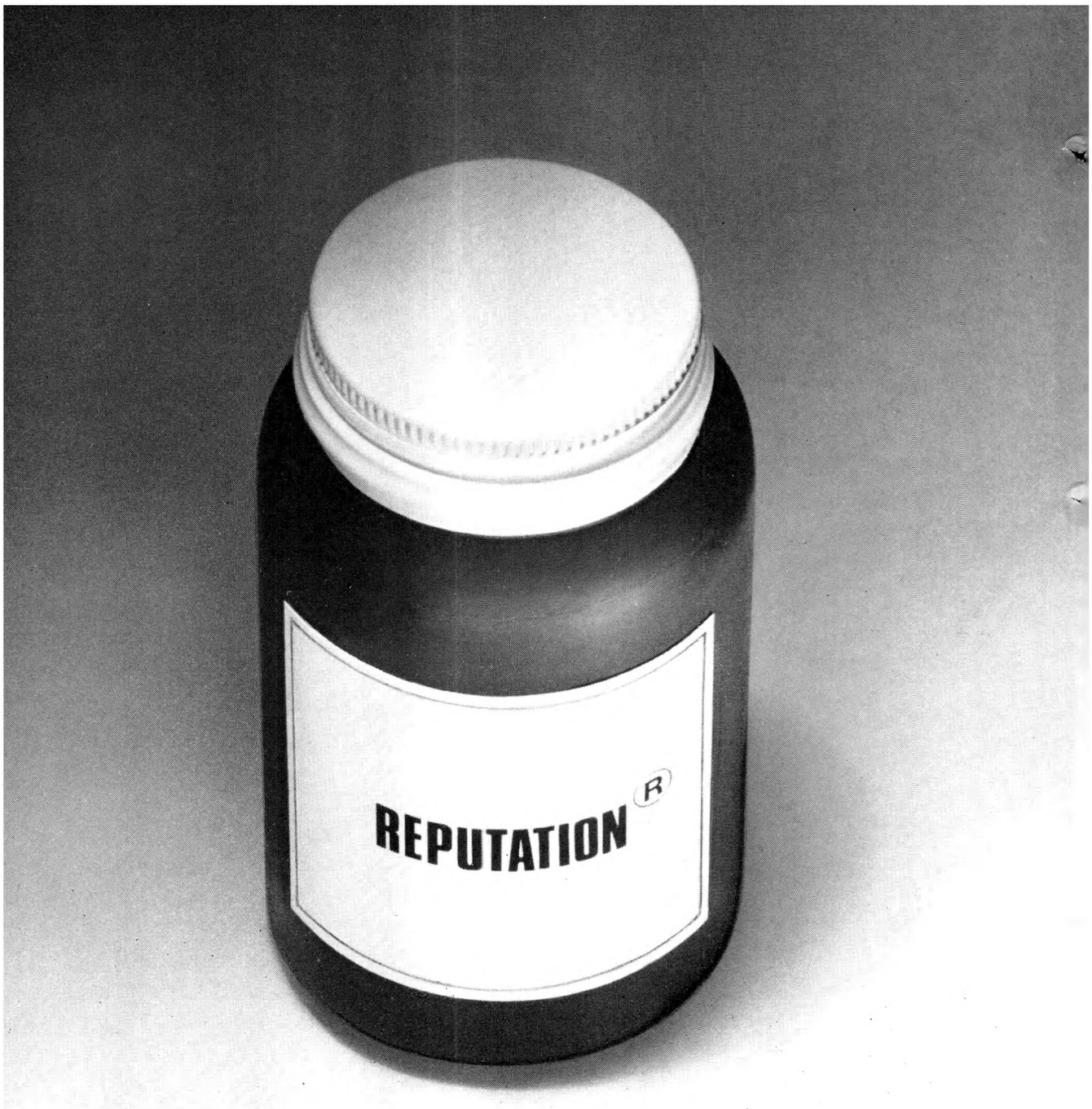


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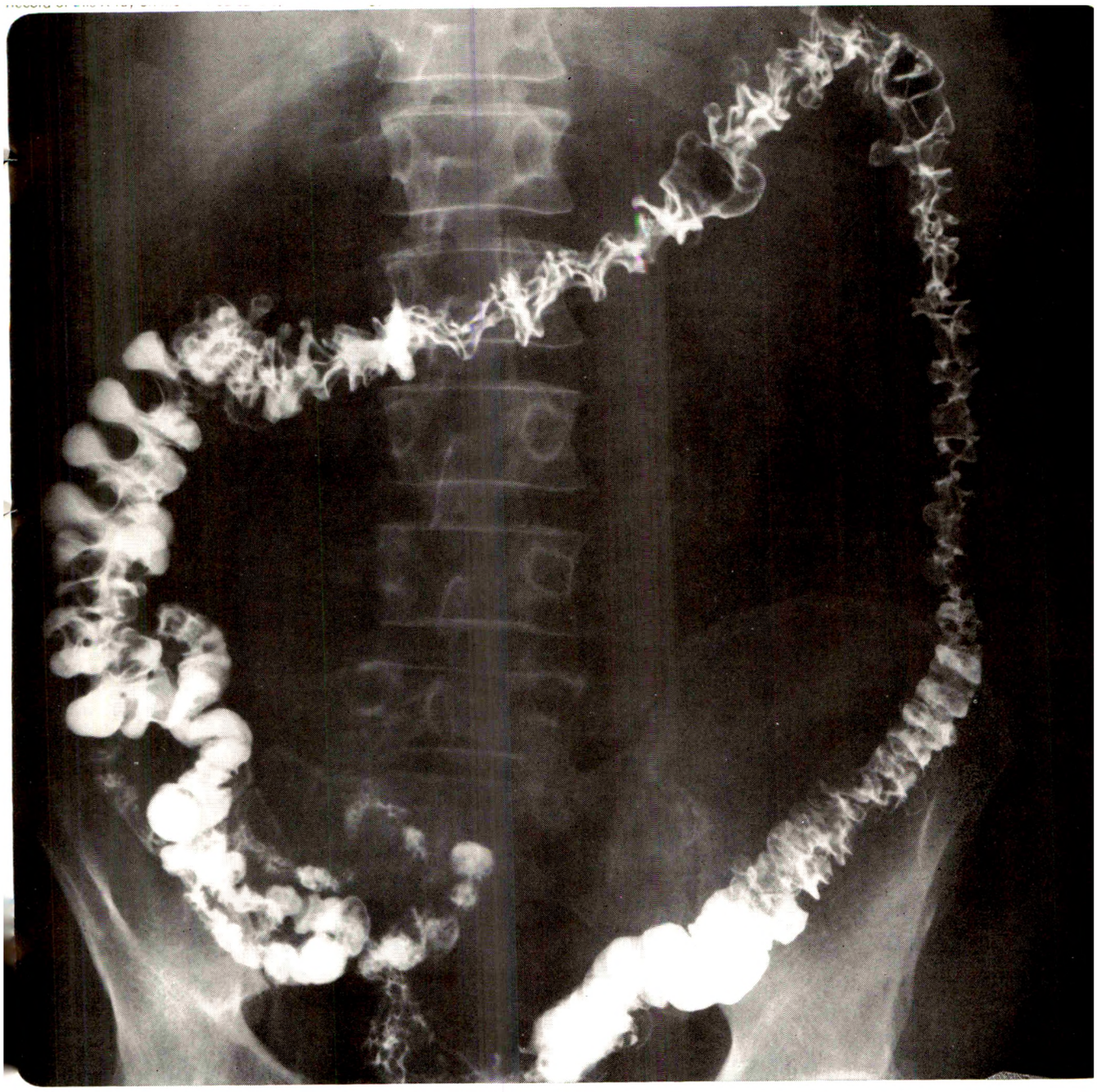
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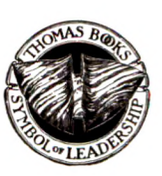
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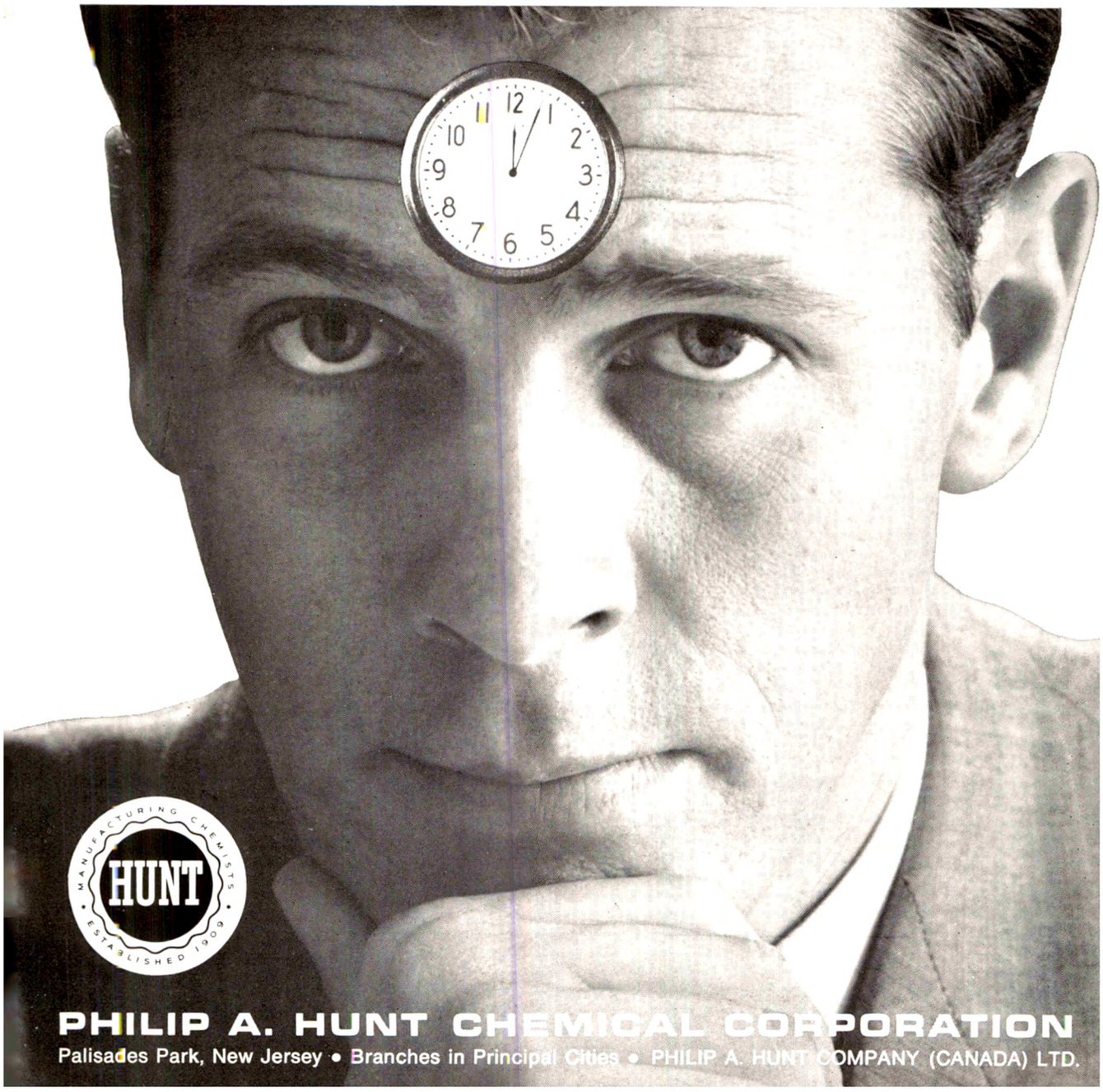


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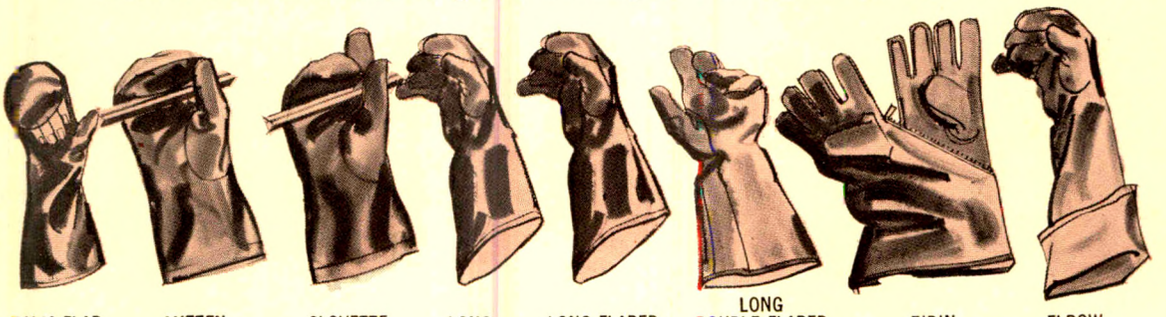
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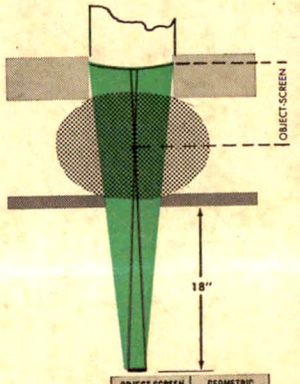
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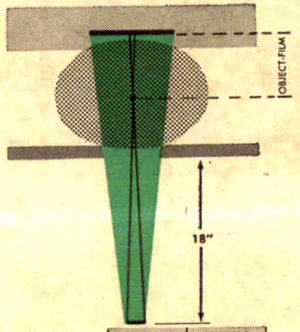
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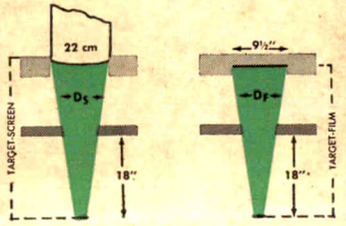
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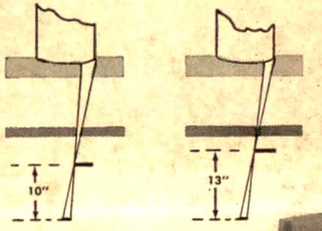
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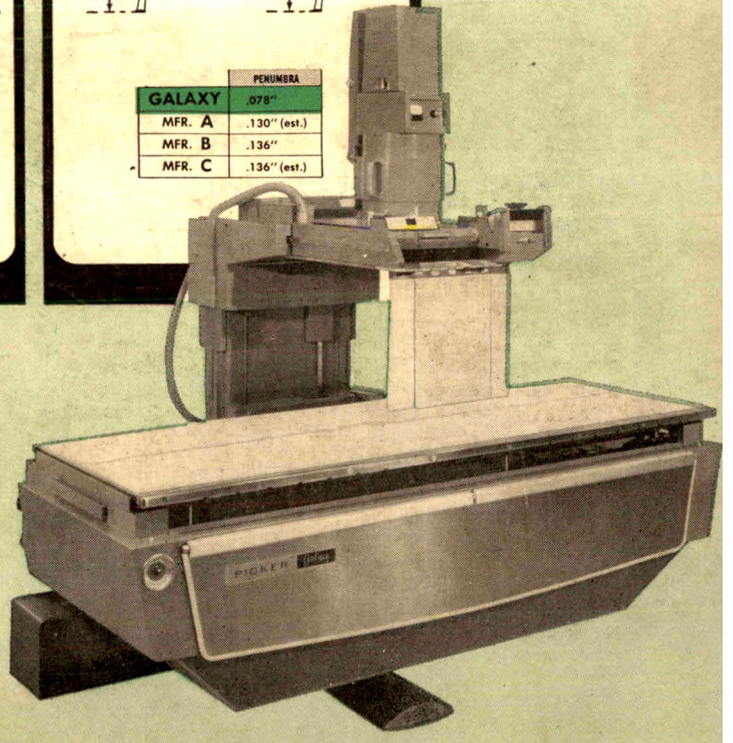
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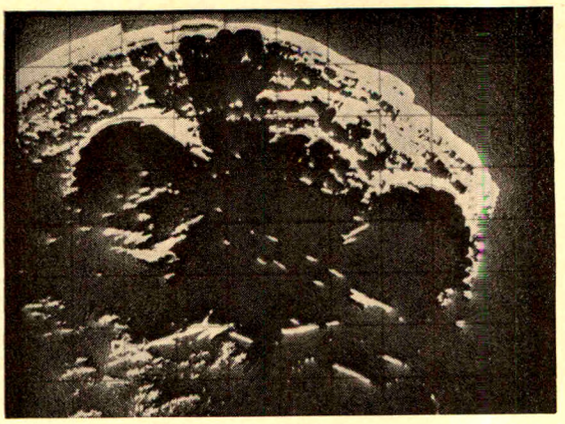
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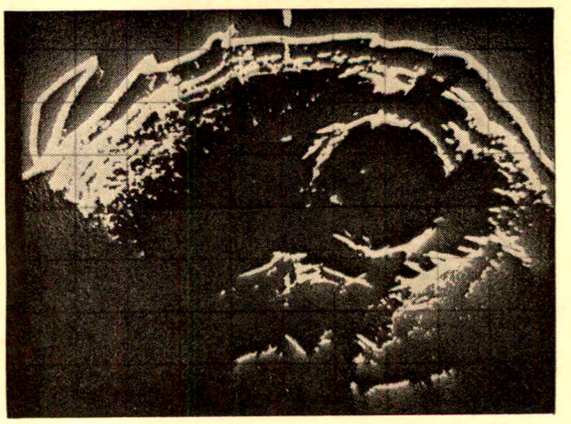
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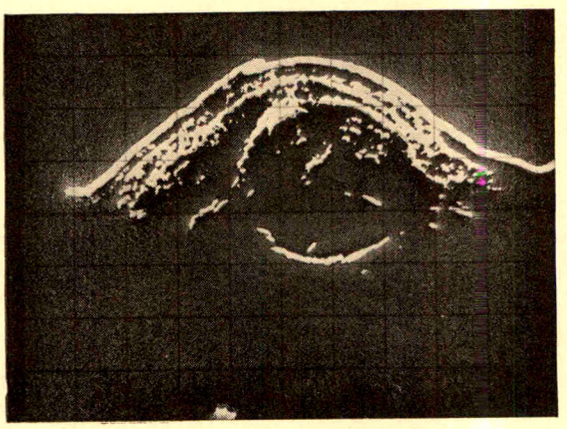
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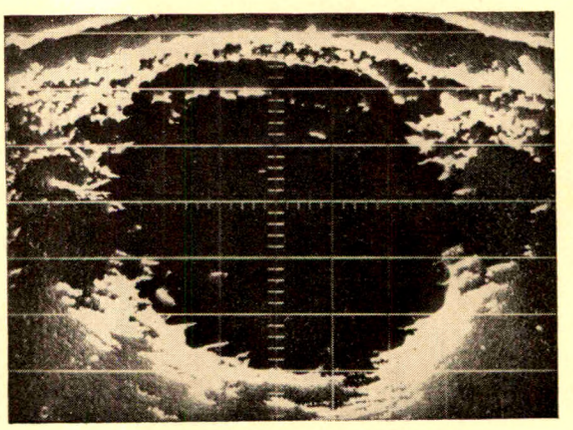
Twin Pregnancy. Contour of one of the heads to right above Symphysis, that of the other to left in fundus, Longitudinal Scan 3 cm left of Umbilicus.
Courtesy of Downstate Medical Center.



Fetus In Utero. Pregnancy 31st Week, Transverse Scan 5 cm above Umbilicus.
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Fetus In Utero. Cephalic presentation, Pregnancy 34th Week, Transverse Scan 10 cm below Umbilicus.
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Malignant Ovarian Cyst. Transverse Scan.
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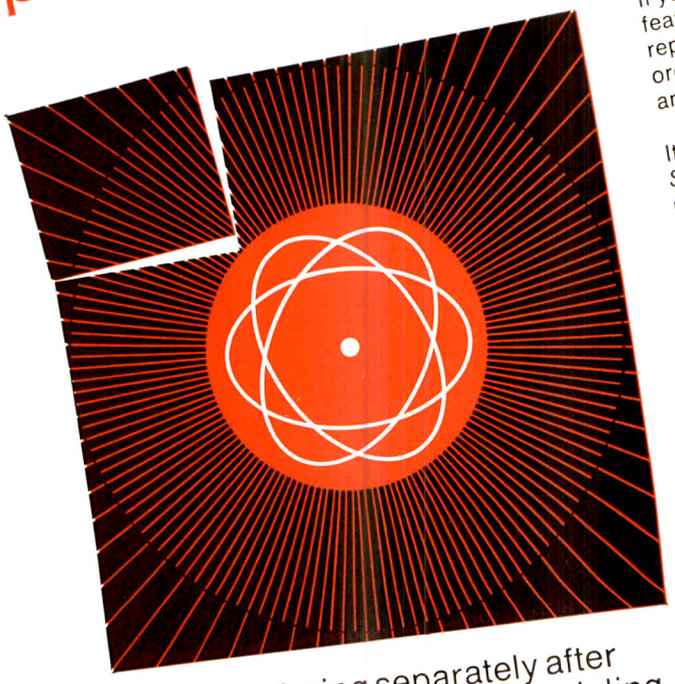
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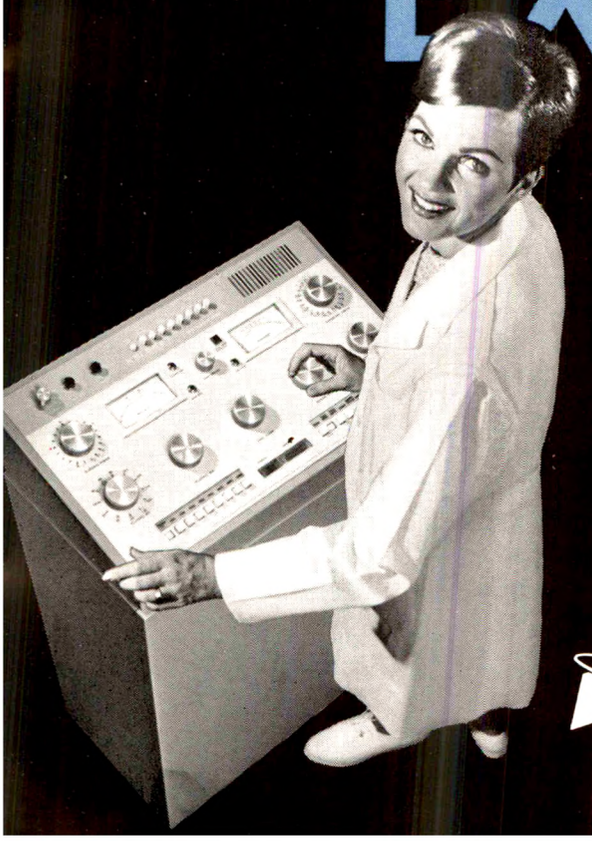
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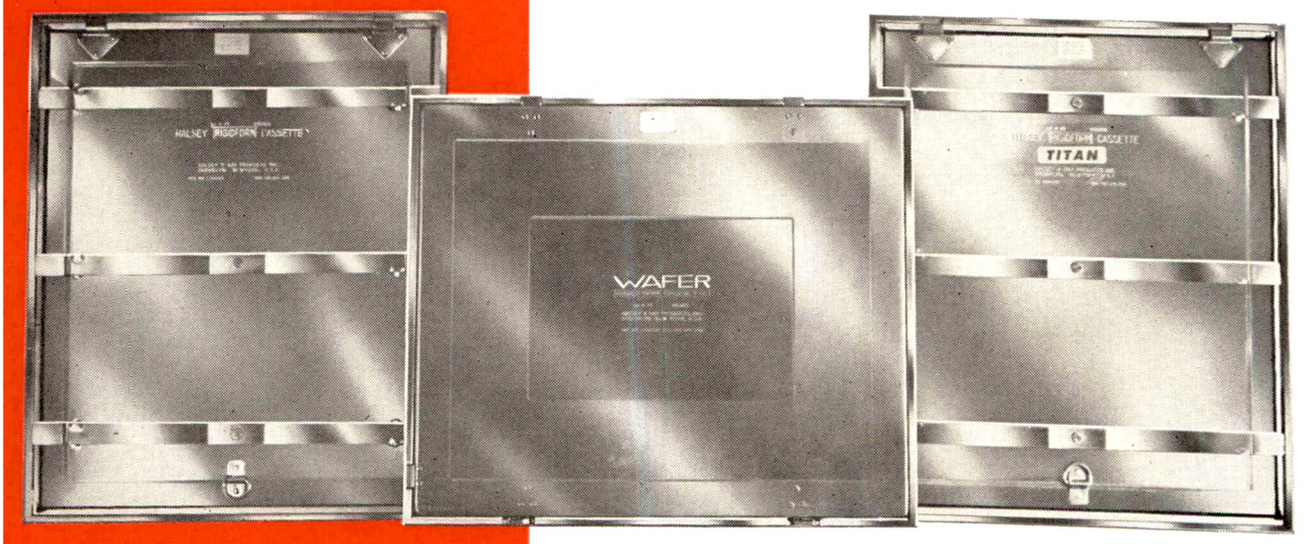
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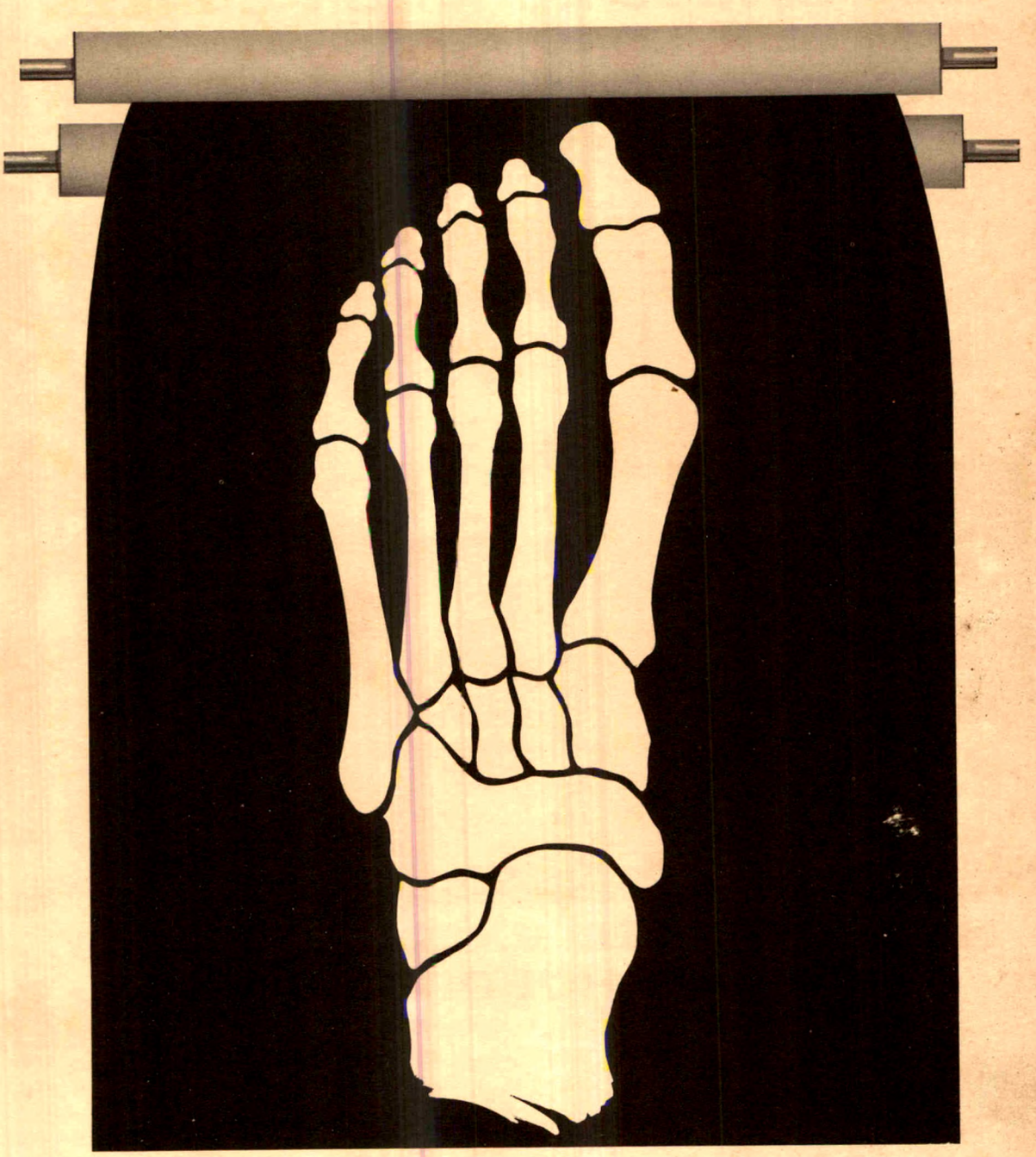
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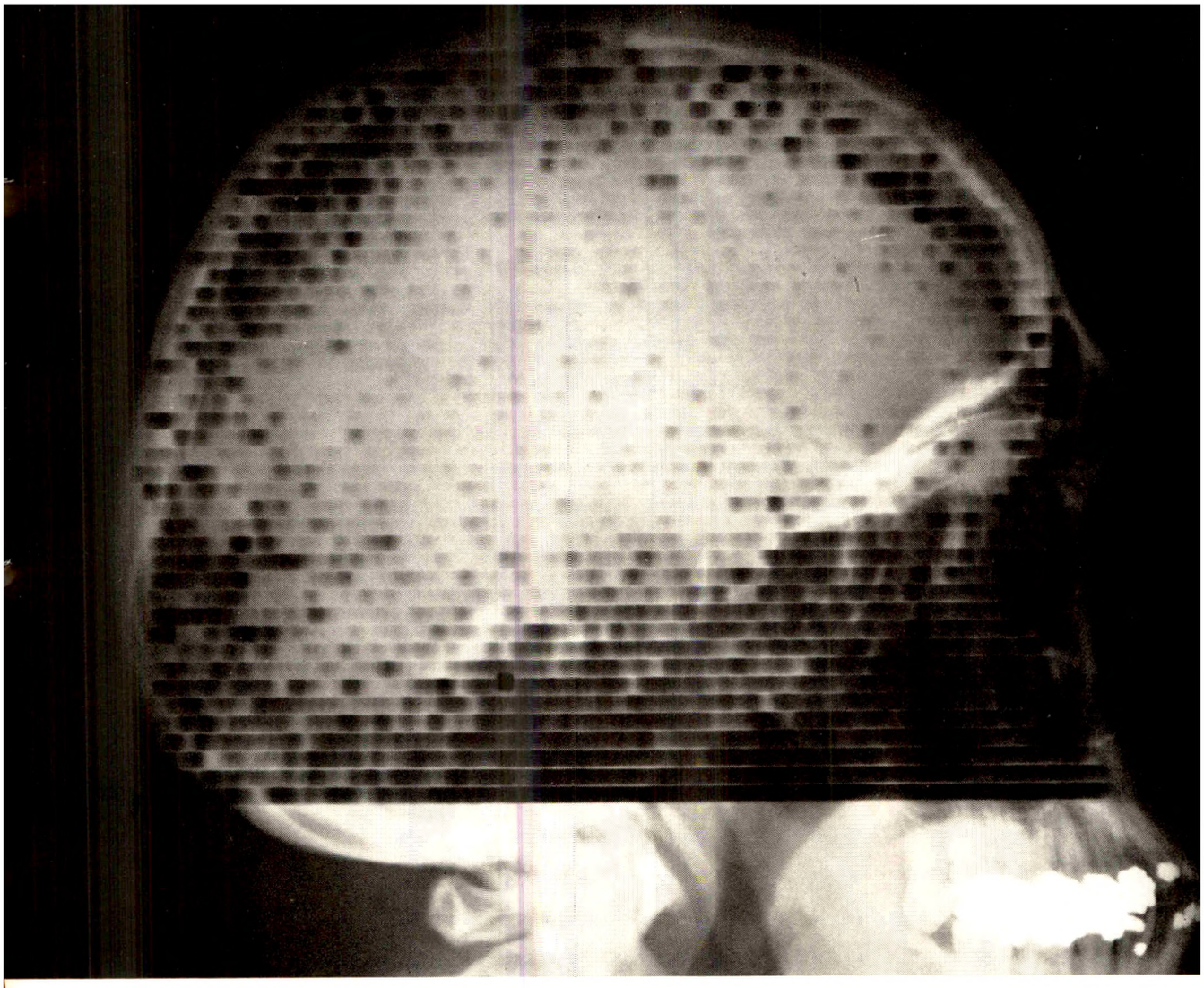
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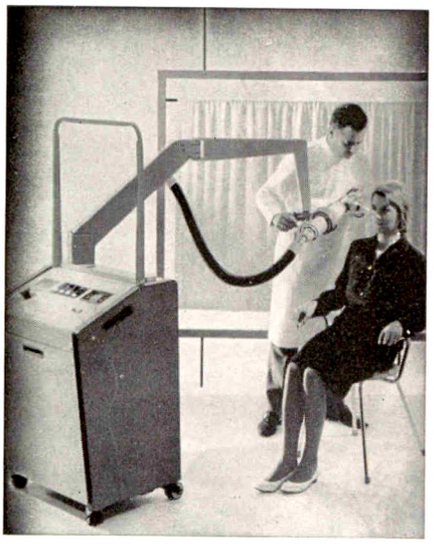
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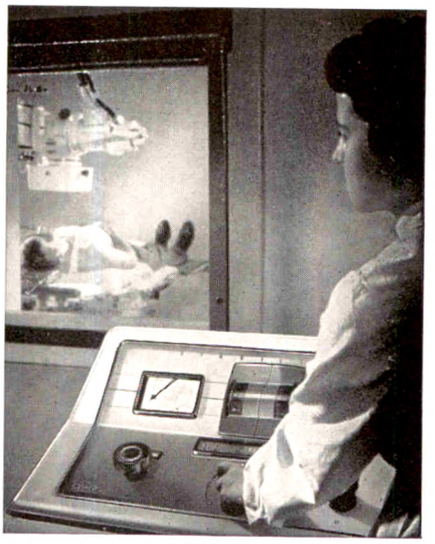
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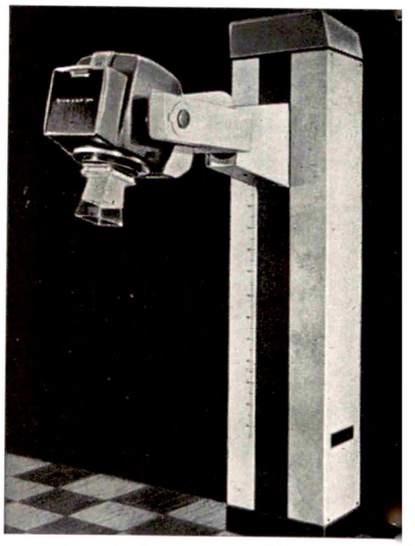
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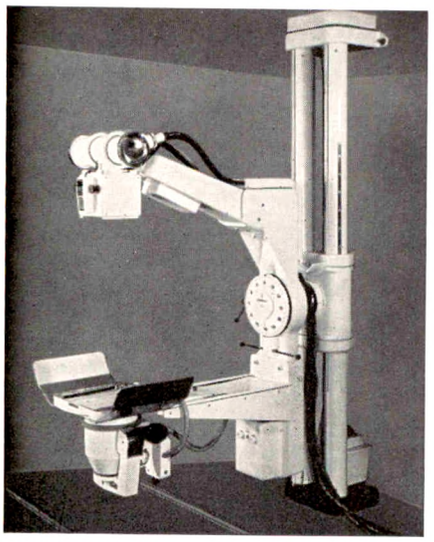
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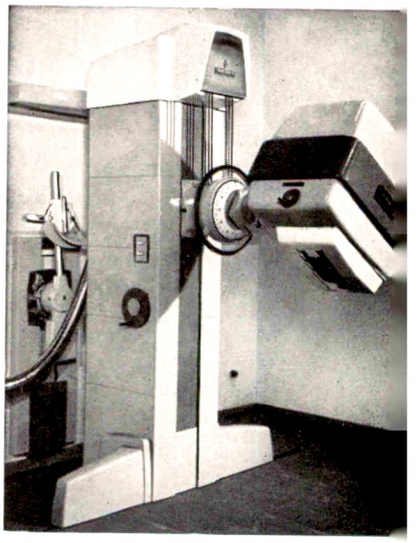
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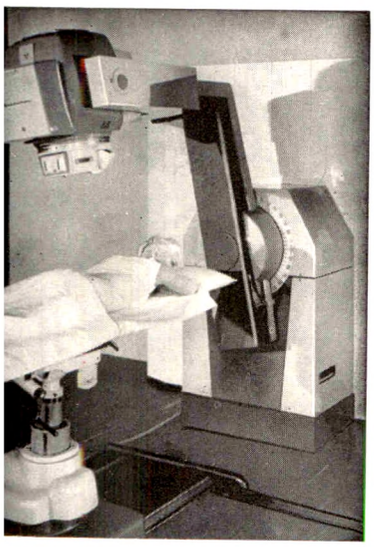
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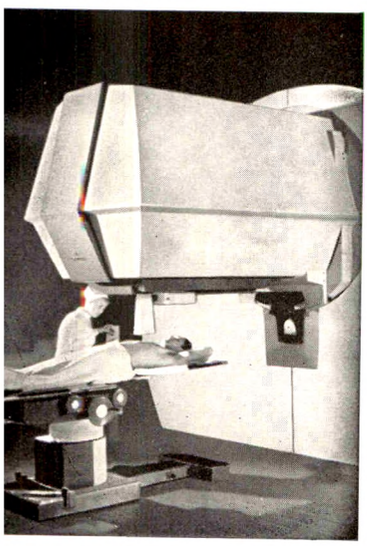


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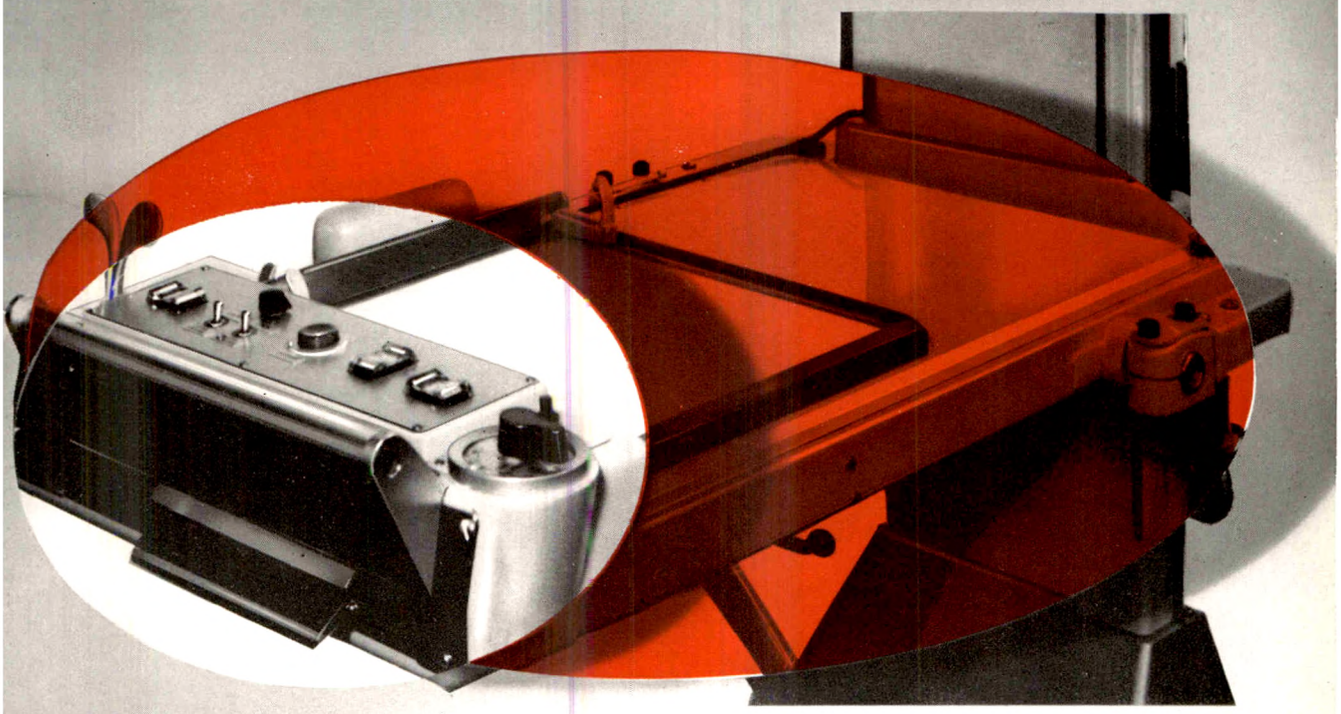
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CONTRAINDICATIONS—Contraindications to hysterosalpingography include the presence of severe vaginal or cervical infections, existing or recent pelvic infection, marked cervical erosion or endocervicitis, and pregnancy. The procedure is contraindicated during the immediate pre- or post-menstrual phase. SENSITIVITY—If indicated in the patient's history, an intracutaneous skin test or sublingual absorption observation may be done with 0.1 cc SALPIX. WARNING—Not for intravenous use. ©OPC 1966

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THE DUPLEX III
SPOT-FILMER CONTROL PANEL

The Scholz Duplex III Spot-Filmer is the Radiologist's First Choice!!

The Duplex III Spot-filmer features the ease and expedience of *full automation* and the optimum convenience of front end loading! The suitable grouping of switches, exposure control, and power assist handle facilitate operation where the radiologist appreciates it most!

The Scholz Spot-filmer accommodates, interchangeably, both 8″ x 10″ and 10″ x 12″ cassettes and accepts any metal American standard or wafer cassette. The Duplex III may be adapted to tables of *any* manufacture and is designed to accept 6″ or 9″ Image Intensifiers of *any* manufacture. The easy removal of the switch panel and cover plates make the Spot-filmer readily accessible for service, while retaining slim-line and compact appearance!

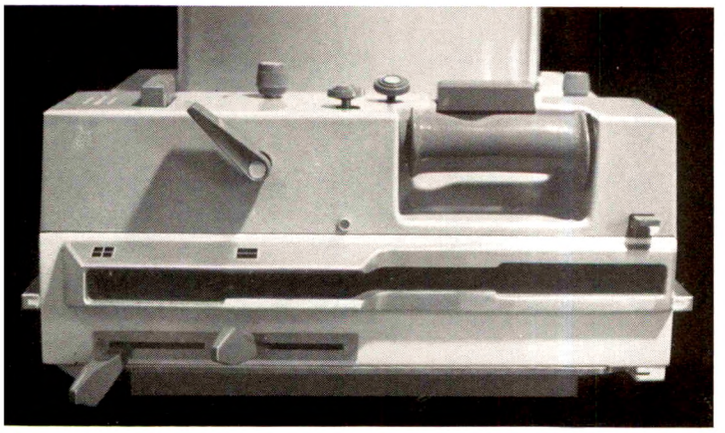
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The NORELCO Diagnost 70 System





Because the image intensifier, spotfilm device, and TV camera are supported by the 90°/90° table, new versatility, breadth of application, and ease of operation are possible with the Diagnost 70 system. Superior TV and spotfilm images, along with the "all-purpose" design of the Diagnost 70 table make the system ideal for a wide variety of examinations.

DIAGNOST 70 Table

- Continuously variable tilting speed—between 15 and 60 seconds for 90°—with lock-in switch at medium speed, and automatic stop with override at horizontal.
- Smooth, silent, tilting and tabletop movement, jolt-free starts and stops.
- Motor-driven "floating" tabletop: Lateral travel—±4" total, with automatic centering; longitudinal travel—±20" total, and an additional 20" extension toward the foot with table in horizontal position.

SCOPOMATIC 71 Spotfilm Device—"Scopo 71"

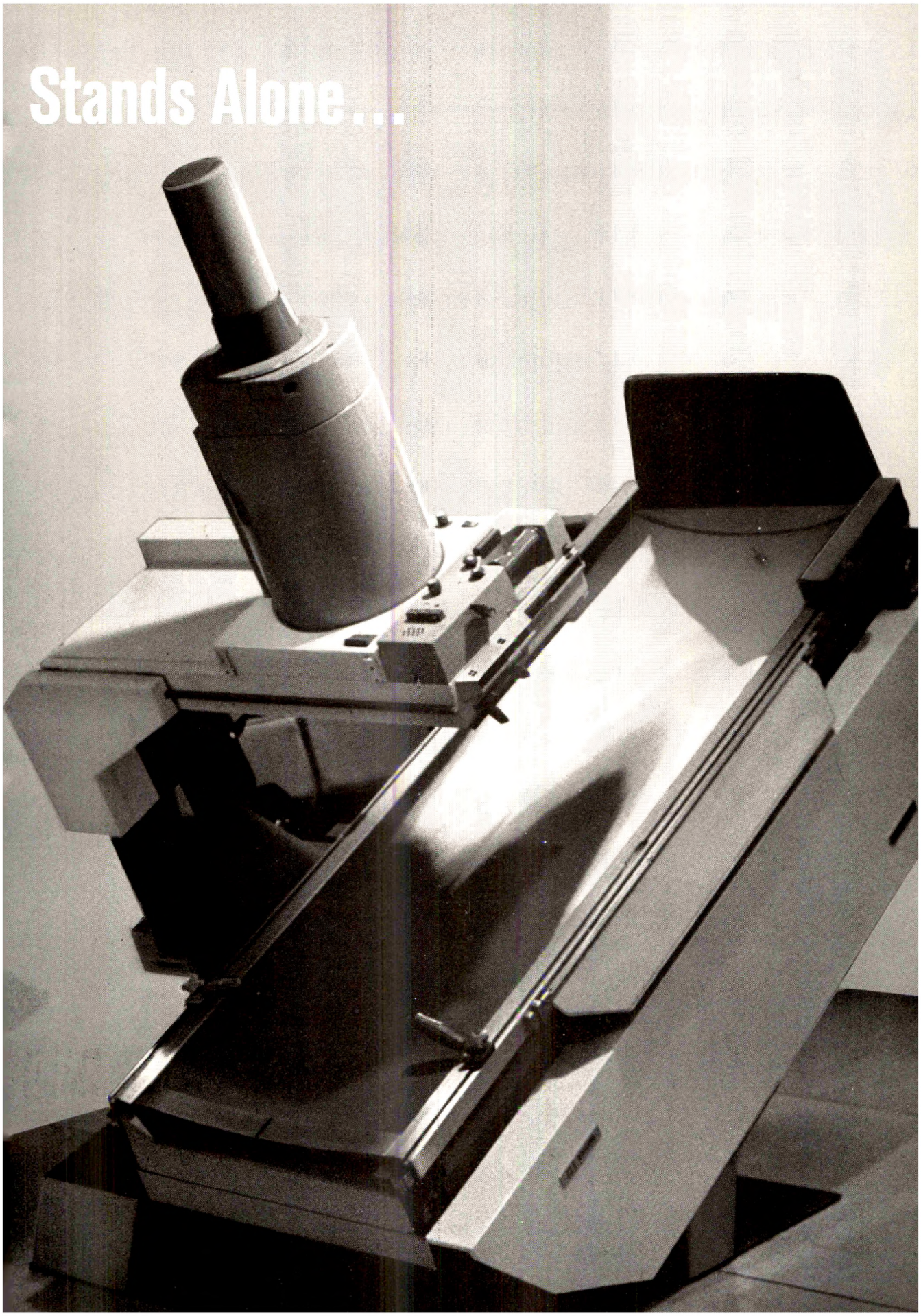
- Spotfilm programming is virtually automatic. The automatic collimator is controlled by the spotfilm program. The spotfilm is automatically programmed according to cassette size and selected masks. Cassettes are automatically centered on the spotfilm device. When an exposure is taken the collimator is automatically adjusted to the selected format size.
- During fluoroscopy, you may adjust fluoroscopic field to any size within the limits of the intensifier input screen. At exposure, beam is automatically collimated to preselected format.
- Fluoroscopy stabilizer with three-level brightness control ensures images of diagnostic clarity on the TV monitor, even during spotfilm exposure.
- All intercom, table and program controls are all handily located on the spotfilm device which is easily parked out of the way for over-table exposures or for patient access.

The "Scopo 71" spotfilm device, the Norelco 6" or 9/5" image intensifier and TV camera are self-suspended—integrated with the Diagnost 70 table into a compact package which is easy to control and manipulate.

Norelco® MEDICAL EQUIPMENT

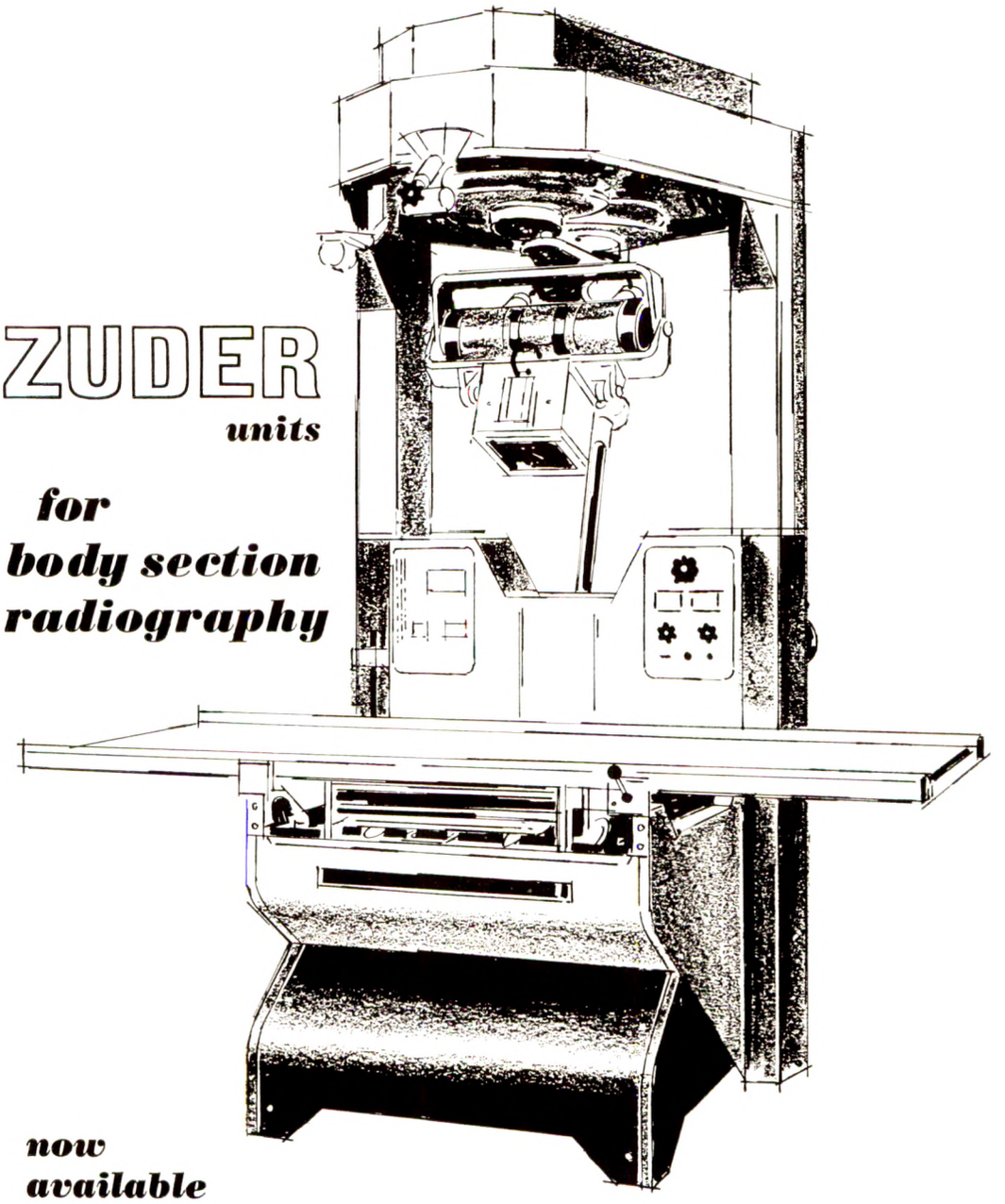
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- Remote Patient Positioning
- Remote Television Viewing
- Remote Bucky/Spot-Filming
- Remote 16-MM Cine-Filming
- Remote 70-MM Spot-Filming
- Remote Compression Control

Here's the diagnostic x-ray system that speeds patient handling, eliminates cumbersome lead clothing, while maintaining close patient/radiologist communication.

for High Volume Work Loads

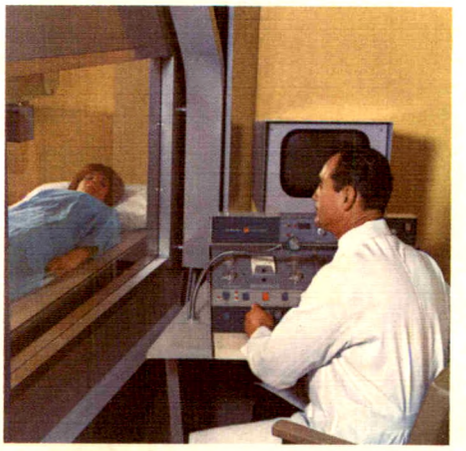
TELETROL II

DIAGNOSTIC X-RAY SYSTEM

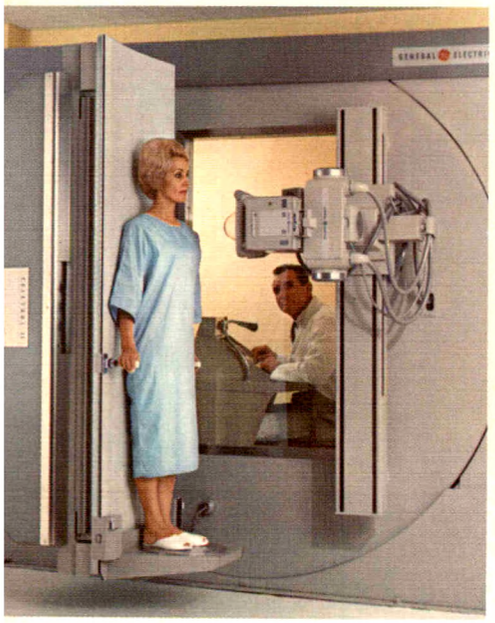
Speeds Up Procedures as much as 50%—New diagnostic technics and rapidly increasing patient loads place heavy demands on radiology departments. Unique integration of table, generator and image presentation components into one compact system allows for easy accommodation into most existing rooms without major alteration. One radiologist can perform a variety of procedures—brightly intensified fluoroscopy, 16-mm cine-filming, 70-mm spot-filming and Bucky radiography—*without ever moving from the convenient, radiation shielded control console.* Patients move through rapidly with consistently efficient results. The generator provides 150 kVp for all radiographic technics with independent fluoroscopic kVp.

The Teletrol II is provided with high performance operational features. New transverse table top movement is independent of Bucky. The radiographic tube is automatically aligned for precision recording because it's coupled to the intensifier. A new 4-on-1 serial cassette tray speeds up filming; also accepts conventional standard cassette tray. Rotating foot rest, shoulder rest, grasp handles and safety harness are furnished as standard features.

New Relicon Television System—Teletrol II is equipped with a new high resolution separate mesh vidicon TV camera, available in 525 or 875 line scan rate, featuring 15 megacycle band width and contrast-improving circuitry. Relicon camera and read-out system are designed specifically for image intensification. The monitor has a full 14-inch screen.



Instant Command Control Console—The ultimate in convenience and equipment response is provided by the Teletrol II control console. Operator maintains close patient contact visually through 30¾-inch x 54¾-inch radiation-shielded window and audibly through intercom system.



Smooth 90-90° Angulation—Teletrol II provides smooth, quiet powered angulation and table-top movement. Table angulates at choice of 2.2 or 4.5 degrees per second with automatic stops at horizontal, Trendelenburg and vertical. Moving top measures 84-inch x 29-inch, easily supports 300-pound patient. Top extends 30 inches off either end and 10 inches transversely for complete patient coverage. New top design is contoured to provide minimum patient-to-film distance for improved detail and sharpness. All positioning of table and patient easily controlled from operator's console.

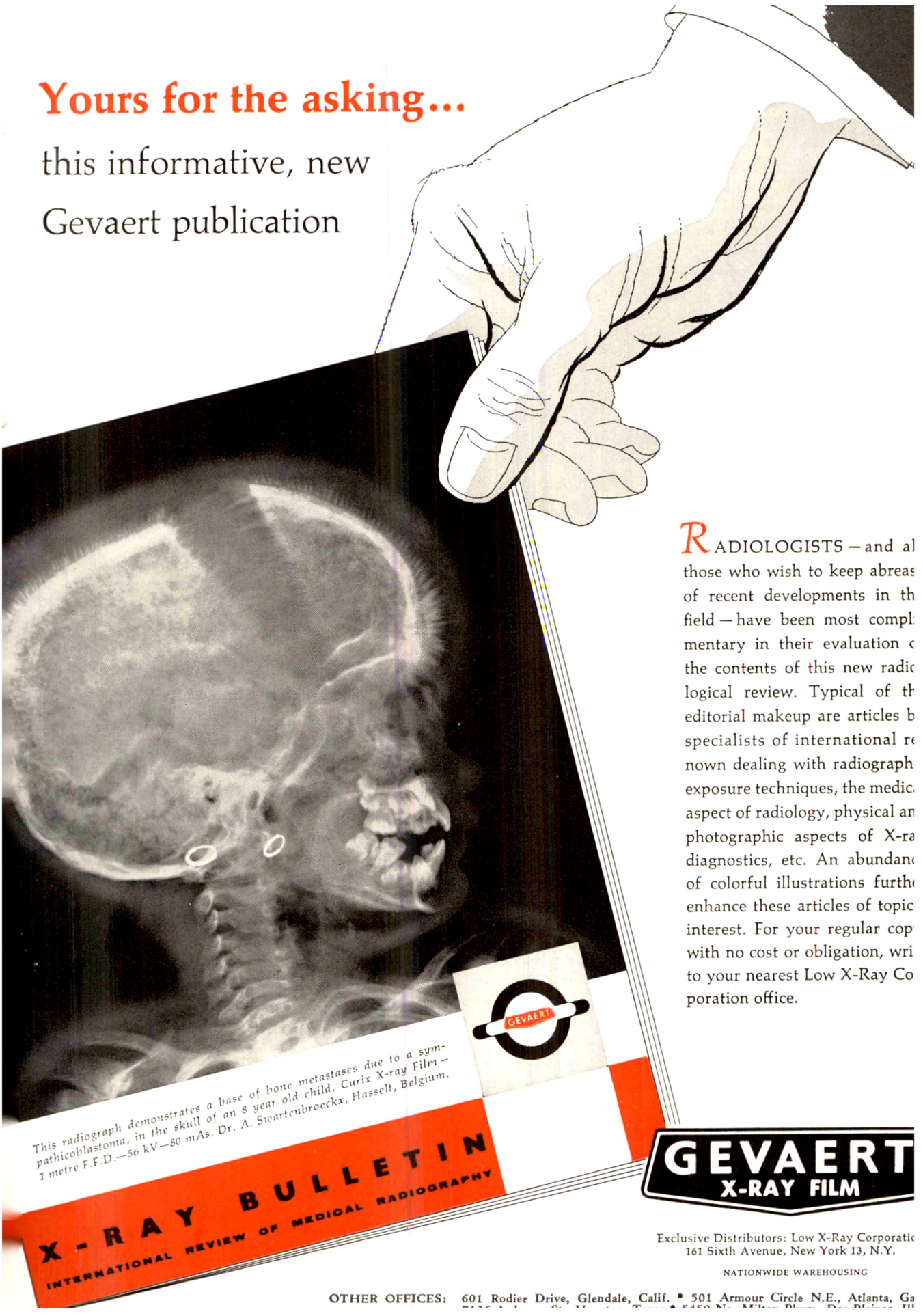


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This radiograph demonstrates a base of bone metastases due to a symphathicoblastoma, in the skull of an 8 year old child. Curix X-ray Film — 1 metre F.F.D.—56 kV—80 mAs. Dr. A. Swartenbroeckx, Hasselt, Belgium.

RADIOLOGISTS — and al those who wish to keep abreas of recent developments in th field — have been most compl mentary in their evaluation c the contents of this new radic logical review. Typical of th editorial makeup are articles b specialists of international re nown dealing with radiograph exposure techniques, the medic aspect of radiology, physical an photographic aspects of X-ra diagnostics, etc. An abundanc of colorful illustrations furth enhance these articles of topic interest. For your regular cop with no cost or obligation, wri to your nearest Low X-Ray Co poration office.

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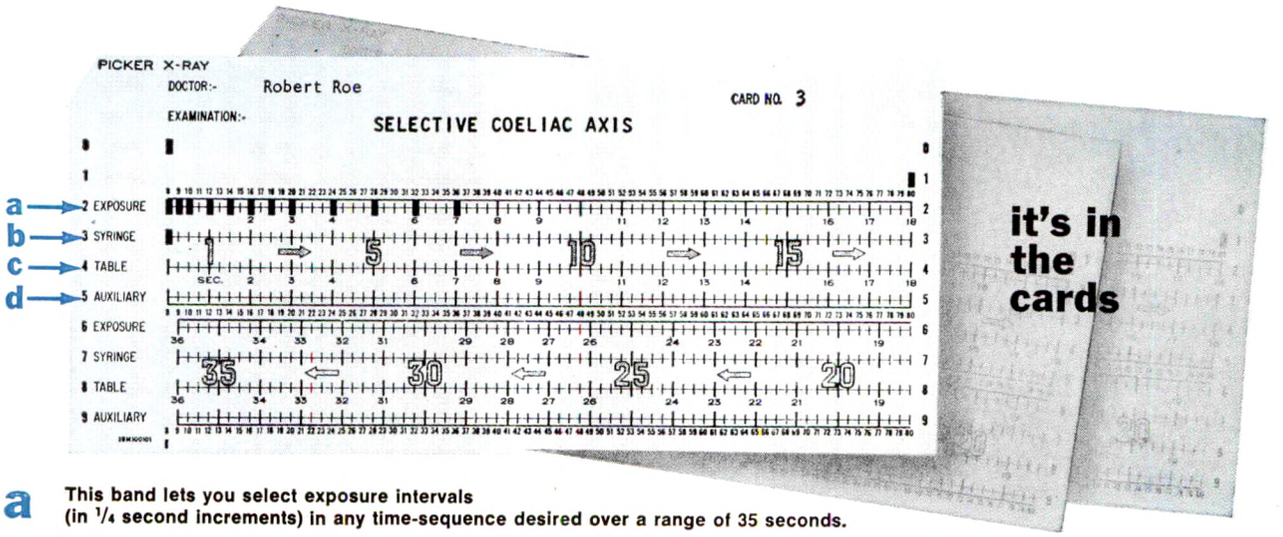
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how computer programming automates serialography in new 420 CP Changer

Remarkable thing about the new Picker 420 CP Cassette Changer is the way simple punchcards (you see a typical one below) take over every operational aspect of serialography. You design the program in advance by punching holes at the desired time intervals for any or all of the action categories shown. Having readied the patient, you simply slip the pertinent card into its slot on the remote control: then start the examination going from that remote station.

The procedure will be carried out exactly as you've punched it, time after time with dependable replicability. On the other hand, should you wish to vary the procedure in any particular, you merely punch a new card.

Great new idea, this electronic masterminding. Simple, versatile, time-saving. Unimpeachably accurate. Best of all, ready to serve you right now.



a This band lets you select exposure intervals (in 1/4 second increments) in any time-sequence desired over a range of 35 seconds.

b This band lets you coordinate injection with exposure: multiple injection pulses can be integrated in any sequence.

c This band shifts the patient to predetermined positions if you're using the companion Picker Pedestal Table, with its motor-driven table top (pictured below).

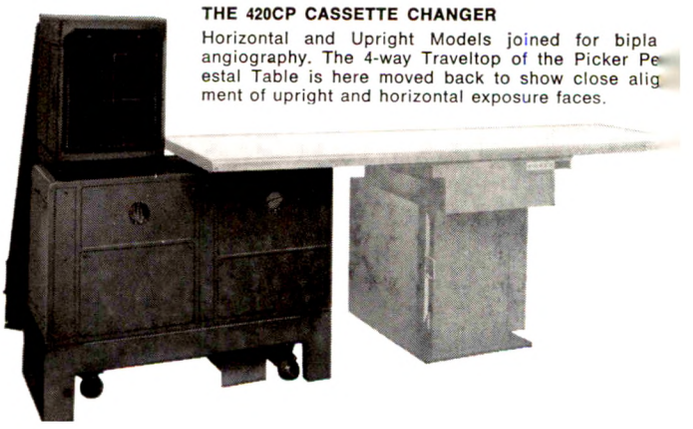
d This band is reserved for any special parallel procedure (e.g., cineradiographic, cardiographic, or whatever) that you'd like to use now, or may develop in the future.

new high in radiographic definition, too because it uses vacuum cassettes

The absolutely uniform overall contact between screens and film attained in the Picker-Amplatz vacuum cassettes yields remarkably detailed radiographs, crisply defined from edge to edge and out to the very corners. Spectacular resolution in cerebral studies, for example, exhibits threadline vessels and capillary stains to great advantage.

Picker x-ray

PICKER X-RAY CORPORATION



THE 420CP CASSETTE CHANGER
Horizontal and Upright Models joined for bipla angiography. The 4-way Traveltop of the Picker Pe estal Table is here moved back to show close alig ment of upright and horizontal exposure faces.

same day re-examination in oral cholecystography

obviously practical, but... diagnostically valuable?

UNSATISFACTORY opacification after routine cholecystography doesn't necessarily mean the gallbladder is diseased. Poor absorption of the contrast agent from the gastrointestinal tract, or the inability of the liver to conjugate and excrete it, might just as well be the cause.[1]

'Nonopacification' is not a condition you can treat

To determine the cause of nonopacification, most physicians request re-examination. There are two ways this has been done by the oral route in the past:

- by starting all over again at a later date — and sometimes doubling the dose of contrast agent on the second try;
- by administering more contrast agent the evening of the first unsuccessful examination (and, again, sometimes doubling the dose) and repeating the study the following day.

Both these methods share two inherent disadvantages. They take a good deal of time, and they require the patient to take a good deal of oral contrast agent. The amount given assumes clinical importance because it has been reported higher doses may result in considerable patient discomfort because of diarrhea and other significant side effects.[1]

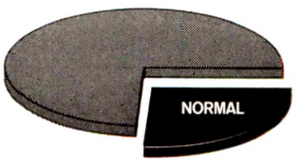
Recently it's been demonstrated, however, that the use of Oragrafin Calcium (Squibb Calcium Ipodate) permits repeat films with significant cuts in both time and total dosage.

Oragrafin Calcium—absorbed so rapidly you can re-examine the same day

"The advantage of the calcium ipodate method is that the examination can be completed in five additional hours with a limited dose of contrast agent."[1]

The method is as productive as it is simple. If the initial opacification is unsatisfactory, the patient is given 3 Gm. of calcium ipodate. Films are repeated 5 hours later. Here are the results of a recently published study on same day re-examination using Oragrafin Calcium:[1]

ANALYSIS OF ORAGRAFIN CALCIUM REENFORCEMENT
IN 76 CASES OF UNSATISFACTORY INITIAL OPACIFICATION



Positive information 24 { Normal by present criteria 20 / Cholelithiasis 4
Abnormal gallbladder (by inference) 52

Correlation of x-ray findings and surgical data was excellent. Because many patients were elderly or had complications contraindicating it, surgery was performed in only 13 cases, with these results: Stone — 6; Liver metastases — 3; Carcinoma of pancreas — 1; Carcinoma of gallbladder — 1; Cirrhosis — 1; Normal — 1

Had the initial failure of opacification been assumed to be due to gallbladder disease, the 20 patients (26%) found normal by re-examination might have been erroneously diagnosed and might have undergone unnecessary surgery.

"Same day re-enforcement oral cholecystography utilizing calcium ipodate . . . is a rapid, accurate, low-dose method of obtaining additional information about a gallbladder which is unsatisfactorily opacified following routine cholecystography."[1]

There are other advantages to such rapid absorption. Even without prior preparation of the patient, both cholangiography and cholecystography can be performed on the same day. Optimal concentration in the hepatic and biliary ducts usually occurs within 1 to 3 hours. Although the gallbladder is optimally opacified approximately 10 hours after ingestion of Oragrafin, diagnostically valuable information can often be obtained within 5 hours or less.

Dosage and Administration: For oral combined cholangiography and cholecystography: *Same day* — Oragrafin Calcium Granules — 2 packets 1 hour before initiating examination. *Overnight* — Oragrafin Calcium Granules—1 packet or Oragrafin Sodium Capsules (Squibb Sodium Ipodate) — 6 capsules 10 to 12 hours before radiography, plus an additional packet of Granules one hour before examination.

Supply: Oragrafin Calcium Granules — single-dose foil packets of 3 Gm of calcium ipodate granules, providing 61.7% iodine content. Oragrafin Sodium Capsules — 0.5 Gm. sodium ipodate per capsule, providing 61.4% iodine content.

Contraindications: Contraindicated for persons sensitive to oral iodine compounds or for patients with combined renal and hepatic disease or severe kidney impairment. Gastrointestinal disorders (which may result in inadequate biliary secretion of medium) often impair visualization.

Side Effects and Precautions: Both calcium and sodium ipodate are usually well tolerated. Mild and transient nausea, vomiting, or diarrhea sometimes occur; but the incidence can be reduced by using the calcium Granules and restricting the dosage to 3 Gm.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin reactions, and rarely anaphylactoid shock. They are more likely to occur in the individual with a hypersensitivity diathesis. Antihistamines and corticosteroids are used to control these side effects, but the occasional serious anaphylactoid reactions require the immediate use of epinephrine or phenylephrine, oxygen, and intravenous corticosteroids. For full information see Package Insert.

Reference: 1. Crummy, A. B.: Wisconsin M. J.: 65:84, 1966.

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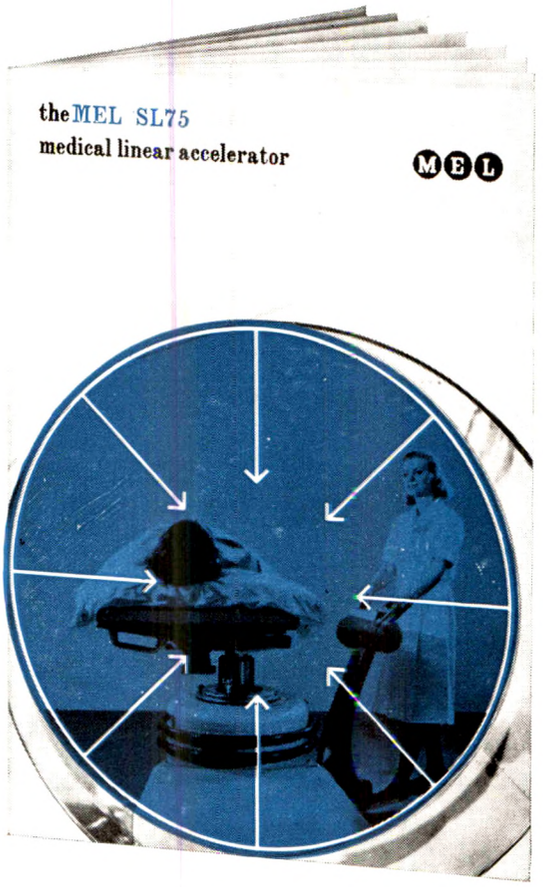
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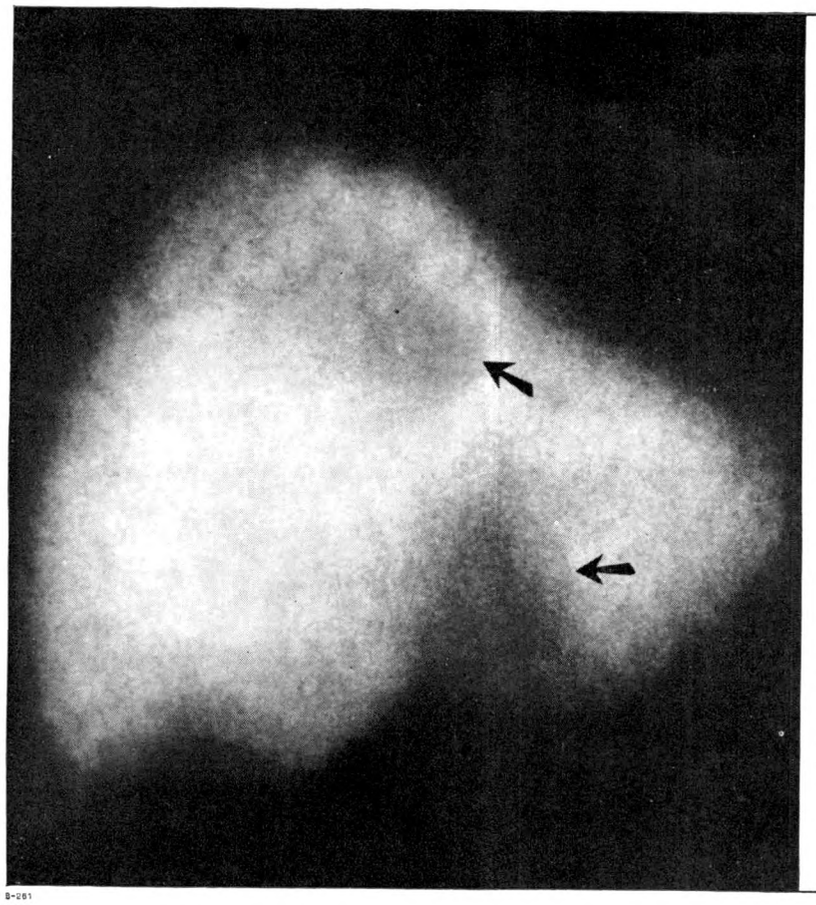
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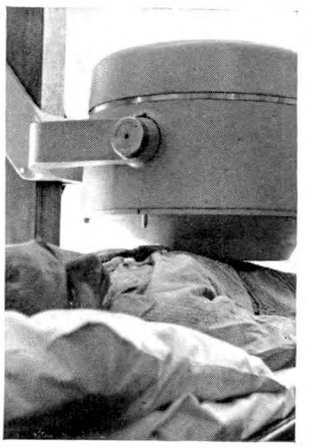
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ORGAN: Liver.
DOSE: 3 millicuries technetium-99m sulfur-colloid.
VIEW: Anterior.
EXPOSURE TIME: One minute, started 15 minutes after injection.
DIAGNOSIS: Metastatic deposits.

Taken with Pho/Gamma Scintillation Camera.

B-261

Liver, abnormal.

Wouldn't you like to be able to locate lesions like these—before biopsy?

The picture shown above is a scintiphoto—a record of isotope distribution made by Nuclear-Chicago's Pho/Gamma® III Scintillation Camera. Consider the advantages of Pho/Gamma for your work.

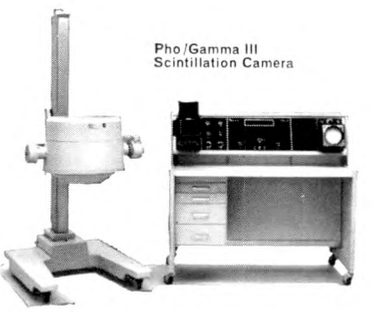
First of all, Pho/Gamma's continuously sensitive view of all of the organ, all of the time, gives you high-speed, high-resolution isotope imaging. The benefits: Maximum patient comfort. Accommodation of heavy patient case loads. Minimal distortion from respiratory and other motions. True dynamic visualization of in-vivo processes by means of rapid-sequence, stop-motion scintiphotography.

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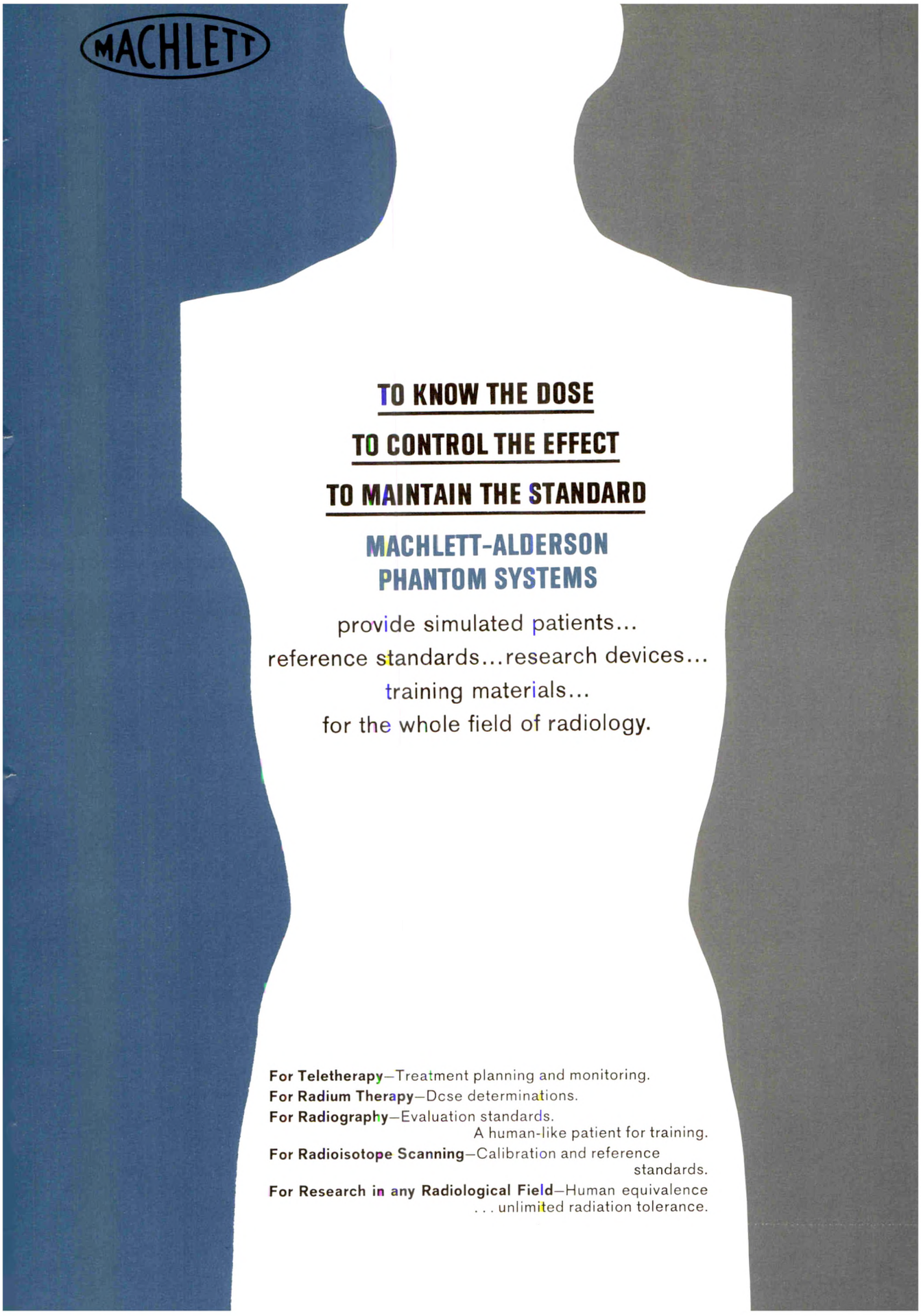


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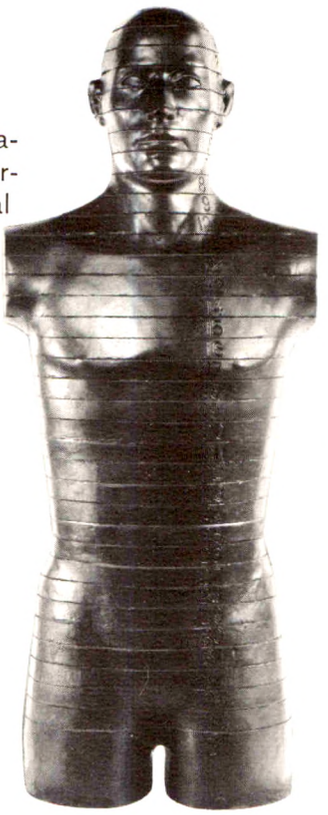
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Head Phantom with hollow brain tumors. Abdominal Phantom, with separate hollow organs and hollow or solid tumors; for scanner calibration, confirmation of diagnoses.



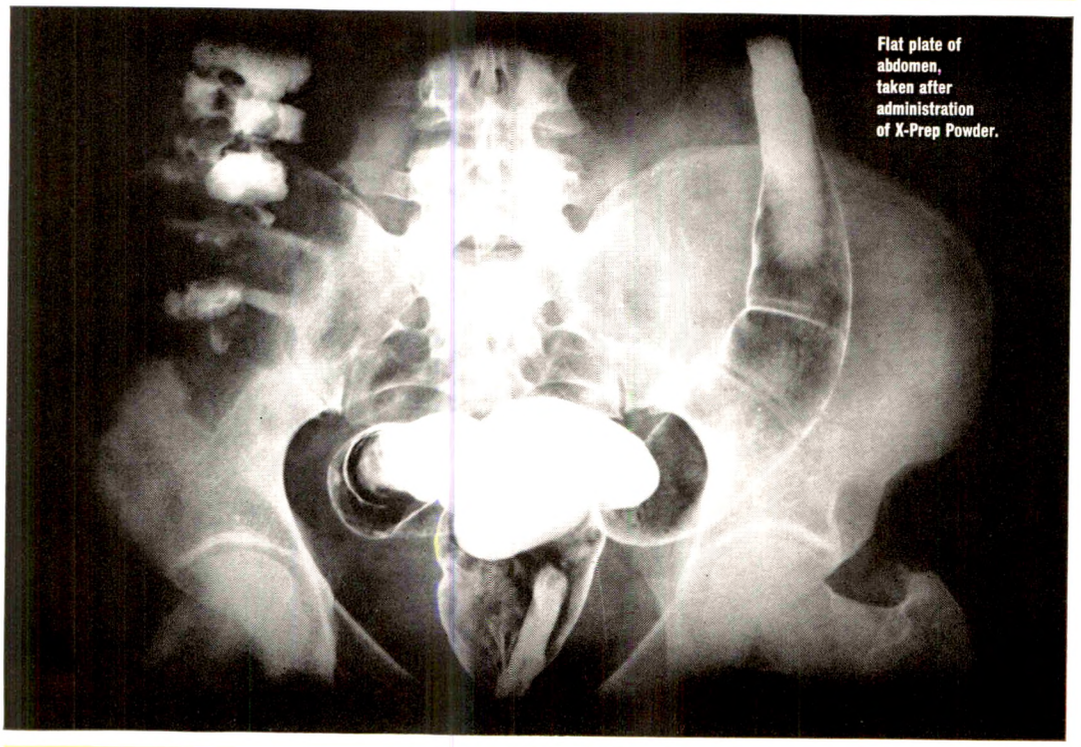
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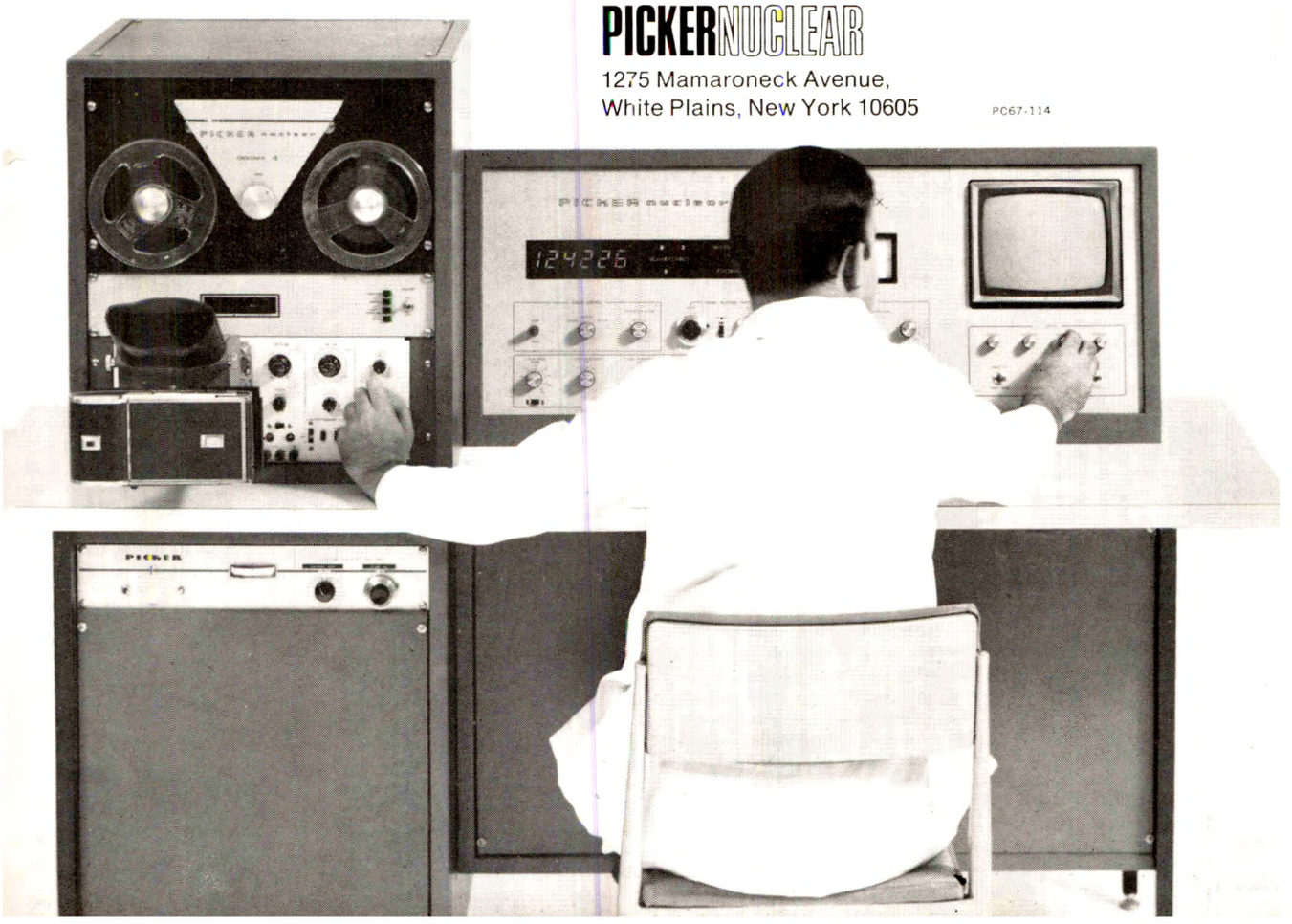
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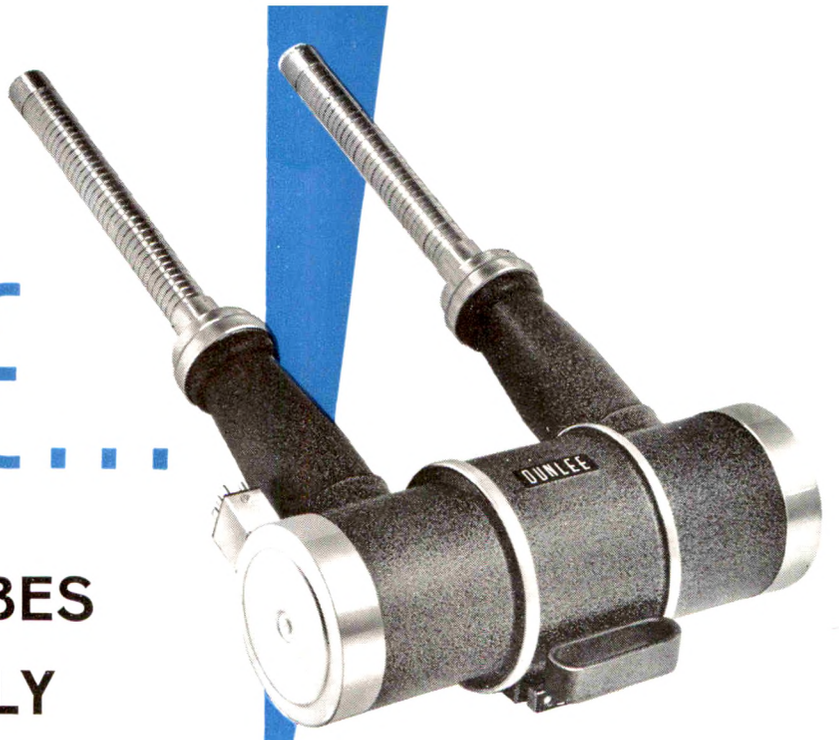
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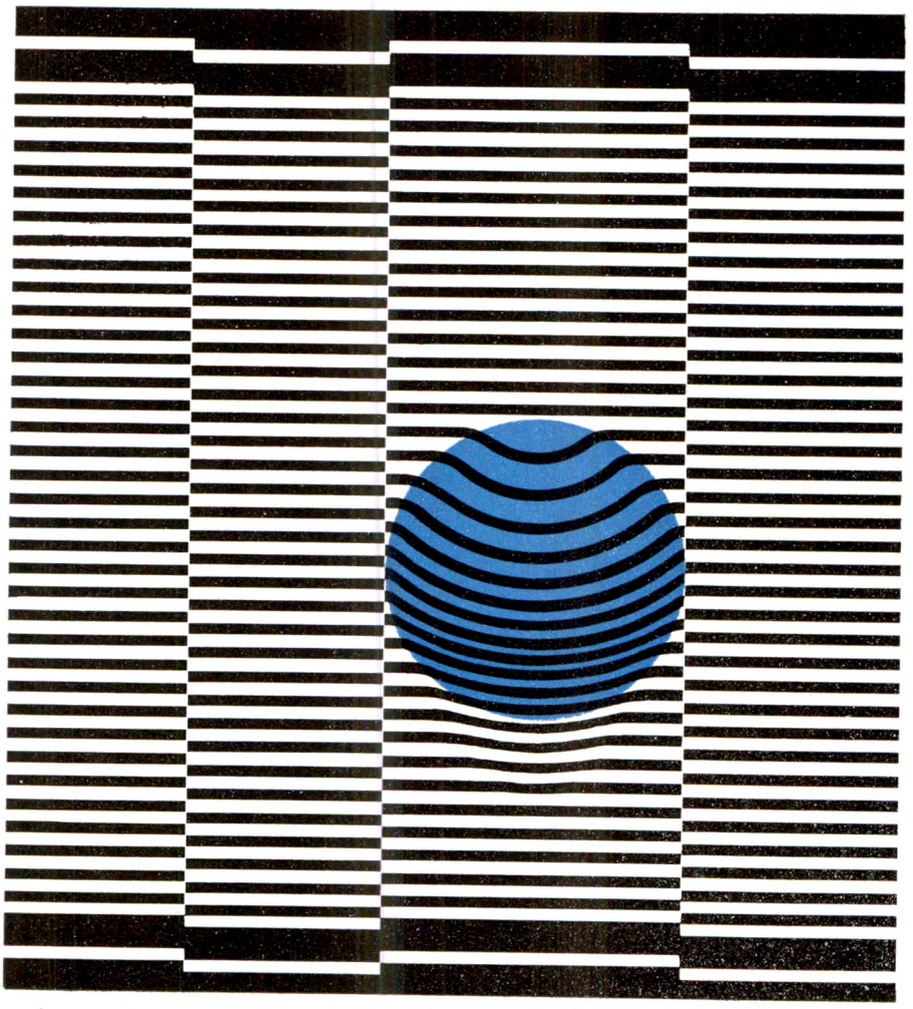
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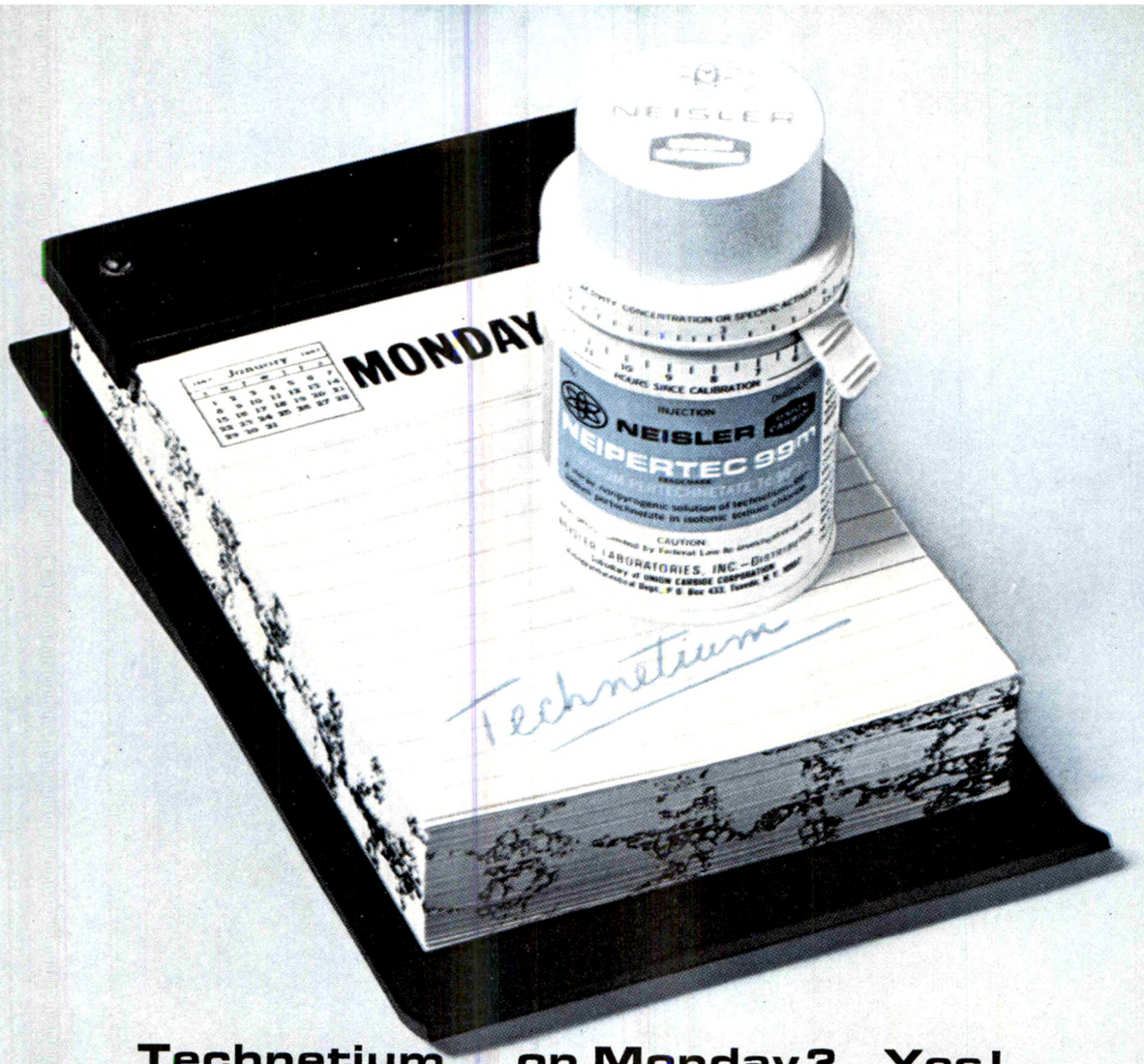
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1. J. G. McAfee, C. F. Fueger, H. S. Stern, H. N. Wagner, Jr. and T. Migita: Tc^{99m} pertechnetate for brain scanning, *J. Nucl. Med.*, *5*:811, 1964.

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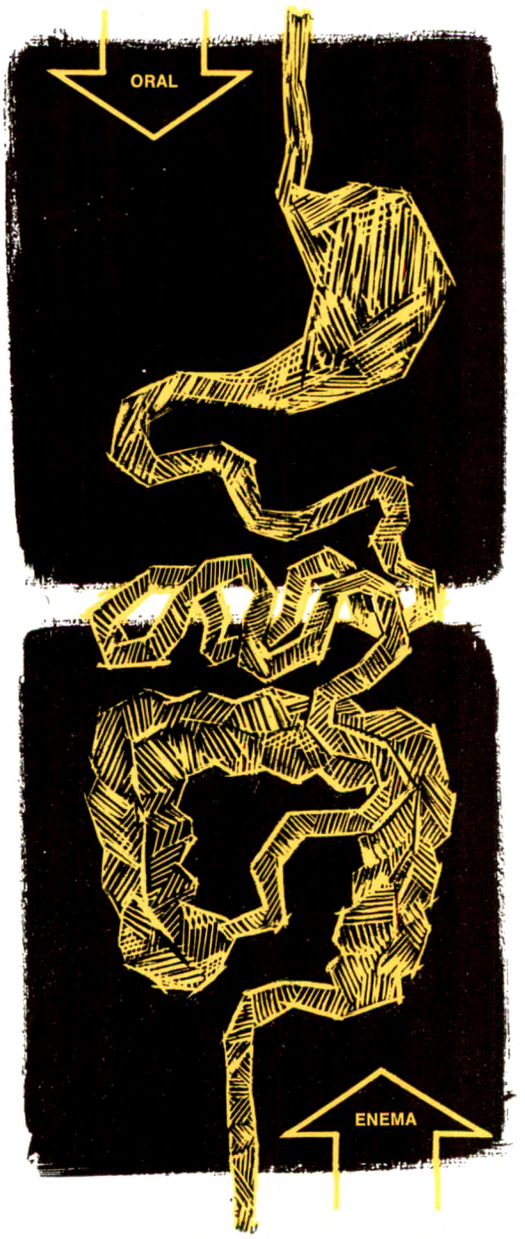
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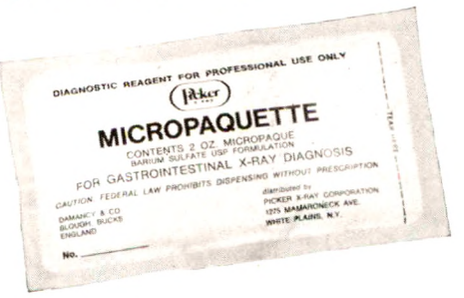
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LOCAL FAILURE IN THE TREATMENT OF MELANOMA

THE JANEWAY LECTURE, 1966

By GORDON McNEER, M.D.,* *and* JACQUES CANTIN, M.D.
NEW YORK, NEW YORK

IN THE light of our present knowledge of the origin and spread of cancer in its curable aspects, control of the primary growth and its first line of defense, the regional lymph nodes, forms the basic tenet of our therapeutic approach. All our efforts must be directed toward this concept since it is only rarely possible to modify the progress of this disease after blood borne metastasis has occurred. Melanoma offers a unique opportunity to evaluate the efficacy of a surgical program, because in its curable phase, this neoplasm is almost always within the field of vision of both patient and physician. For the purpose of this presentation we will confine our remarks to melanoma of the skin.

The recurrence of cancer in or adjacent to the original site of growth demands a re-evaluation of the initial treatment. It is proper, therefore, that we evaluate the methods which have been applied to the control of melanoma which, because of its location on the body's surfaces and because of its unique life history, affords a readily available source of information.

DEFINITION OF TERMS

Local failure means that the primary attempt to control the tumor in its original site has been unsuccessful. It is impossible to differentiate histologically between a cutaneous recurrence of melanoma and a cutaneous metastasis of melanoma (Fig. 1). We assume that a blood borne metastasis has occurred if the new lesion appears distal to the operative site; and, either a blood borne or lymphatic metastasis, if located laterally or proximally (Fig. 2). Multiplicity of lesions implies metastasis and when such lesions appear about the periphery of the treated or untreated primary site, they are referred to as satellites (Fig. 3). Certainly, if the new process appears in the scar or operative site, it must represent a recurrence according to any usual interpretation of the work. All of these terms refer to local manifestations

Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
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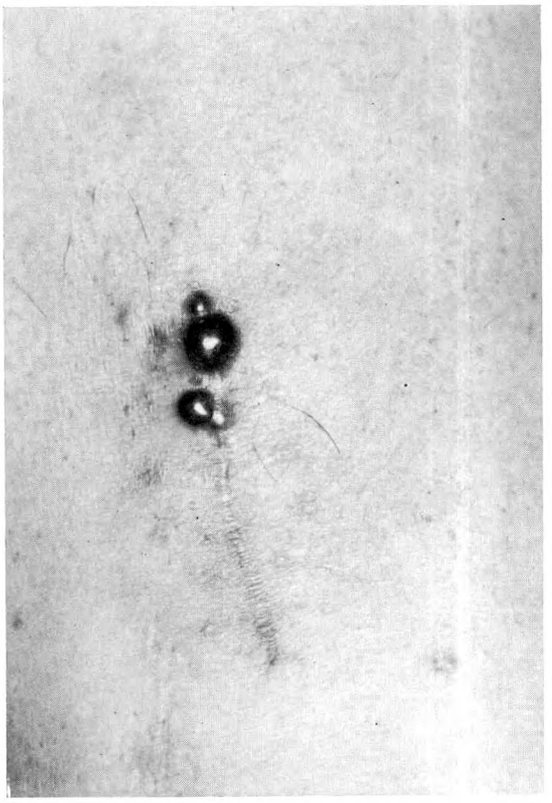


Fig. 1. Local recurrence of melanoma in surgical scar.

of fully aggressive melanoma and their differentiation is meaningless in an evaluation of our inability to control melanoma in its primary site. Hence, all are included in this evaluation of local failure.

THE NATURAL HISTORY OF THE LOCAL BEHAVIOR OF MELANOMA

Attempts to differentiate local metastasis from local recurrence are really academic. It is the nature of melanoma to spread proximally both by direct permeation and by embolism via the superficial and deep lymphatics, whether it be primary or locally recurrent. Although this phenomenon was first brought to our attention by Astley Cooper we are particularly indebted to Sampson Handley[5] and Rouvière[9] for their contributions to our understanding of the anatomy of the lymphatic pathways on the body's surface. In reviewing the illustrated descriptions derived from their separate and original dissections, one is especially impressed by the rich meshwork of the lymphatics of the dermal and fascial structures, studded here and there in a fairly predictable fashion by intercalated nodes. While these lymphatic channels are more closely approximated in some areas (hands) than in others, their unique character is their ubiquity. Handley's dissections illustrate the ease with which these pathways may be permeated by cancer cells which are passed on to the next collecting station, there providing the stasis which favors further permeation via other adjacent lymphatics, either laterally or more deeply. Since melanoma has such a unique ability for lymphatic permeation, it is not surprising frequently to see evidence of local spread as the initial presentation of the



Fig. 2. Local ("in-transit") metastases of melanoma, between primary site in skin of heel and regional lymph nodes.

disease. Furthermore, since we do not know at what stage in its evolution any given melanoma will take on the characteristic of lymphatic permeation, we do not know at any given time whether microscopic spread has already occurred or, at the time of definitive treatment, is in fact occurring. Whereas, it is most logical to assume that lymphatic stasis or even lymphatic obstruction produced by excisional and dissectional procedures is contributive to the phenomenon of local spread, it is likewise the very nature of melanoma to progress in the fashion described above in the absence of any known physical change whatsoever. Likewise, the stasis produced by proximal blockage of the lymphatic vessels by metastatic cancer in the regional lymph nodes may represent an integral feature of the continuing process of local spread. That which most eludes the grasp of one's understanding is the behavior and the timing of the process of recurrence in the individual patient. Why does almost complete permeation of an extremity with metastatic melanoma occur in one patient or, conversely, why does a solitary recurrence appear adjacent to the treatment site 10 to 15 years after apparently adequate local surgery in another?

CLINICOPATHOLOGIC STAGING OF MELANOMA

In order to evolve any meaningful approach to the treatment of cancer and to evaluate end-results, it is necessary to establish criteria for a classification which may be applied to the entire patient population. Significant data will not be forthcoming from a study which includes the management of patients with small superficial melanoma together with those who have disseminated cancer. The presence or absence of metastasis to regional lymph nodes based on histologic and not clinical grounds bears a profound impact on prognosis. Thus, there emerges an obvious division of patients with melanoma into 3 stages based on sound clinical interpretation of the physical findings, confirmed by histologic diagnosis and the presence or absence of histologically proved metastasis to regional lymph nodes. Patients with melanoma have thus been classified at Memorial Hospital for the past several years.[1–4,6,7]



FIG. 3. Satellites of melanoma surrounding untreated primary lesion.

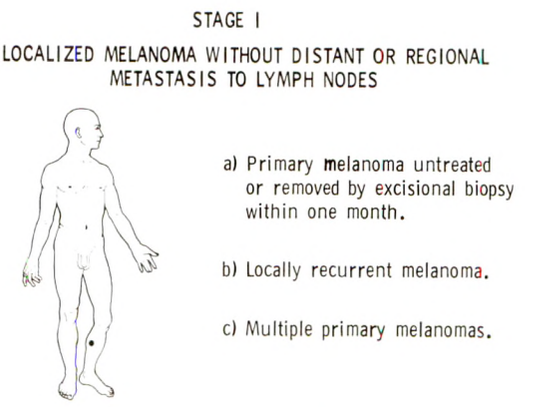


FIG. 4. Sketch of Stage I melanoma.

Stage I (Fig. 4). If melanoma is confined to one surgically removable field, it is considered curable. In Stage I melanoma, the disease is present purely as a local manifestation, as an intact lesion or one recently biopsied. Even when previously treated by ineffectual means, presenting a solitary focus of local recurrence, the disease is still curable and classified under Stage I. Rare instances of multiple primary melanoma are also included in this category.

Stage II (Fig. 5). When melanoma has metastasized to the first regional lymph

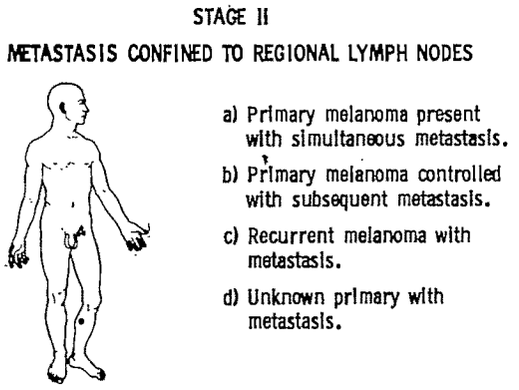


Fig. 5. Sketch of Stage II melanoma.

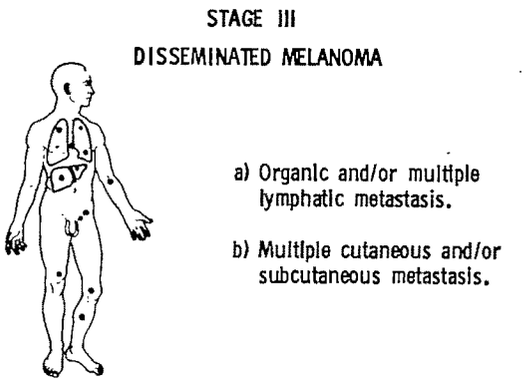


Fig. 6. Sketch of Stage III melanoma.

node station, the prognosis, while diminished, is not hopeless and, hence, the patient is still considered curable. This may still be true when a solitary focus of recurrence in the operative site is also present. Included in this category are those patients who exhibit metastasis to one regional lymphatic drainage system in the absence of a demonstrable primary tumor. As is now well known, a significant number of these patients has apparently been rendered cancer free for many years after adequate dissectional surgery.[1]

Stage III (Fig. 6.) Metastasis to distant organs, to multiple lymph node areas or in a diffuse manner throughout the skin and subcutaneous tissues almost invariably renders the disease therapeutically hopeless. Hence, it is not meaningful to include such patients in the evaluation of a surgical program for the cure of cancer. However, in our present study certain other factors associated with patients in Stage III will be discussed in order to emphasize their impact on delaying ultimate diagnosis and effective treatment.

Classification of All Patients with Cutaneous Melanoma in This Study

During the years 1935 to 1955, 777 patients with melanoma of the trunk and extremities were observed by members of the staff of Memorial Hospital. An additional 137 patients with cutaneous melanoma of the head and neck regions were observed or treated between 1948 and 1955 (Table I). Other patients demonstrating metastatic melanoma of unknown primary origin and those who had undergone adequate surgical treatment elsewhere were obviously not included in this study. A total of 914 patients presented adequate data, including biopsy material and end-result status in each case, for proper analysis. Although

Table I

Local Failure—Recurrence or Local Metastasis Classification of All Patients with Cutaneous Melanoma

Anatomic Location	No. of Cases	Stage I		Stage II		Stage III	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Head and Neck	137	67	49	38	28	32	23
Trunk	240	103	43	99	41	38	16
Extremities	537	297	55	189	35	51	10
Total	914	467	51	326	36	121	13

there is bound to be a certain amount of selection of material in retrospective deliberations, the only conscious prerequisite on our part in this study was that the patient had received definitive surgical treatment for melanoma under the direction of a Memorial Hospital staff surgeon.

Roughly, half of the patients were in the most favorable stage of the disease (Stage I); a little over a third were in a still curable Stage II and the remainder were in the usually incurable Stage III. Individual variations based on anatomic location are shown in Table I, the most significant appearing to be the larger proportion of patients in Stage II for melanoma of the trunk and in Stage III for cutaneous melanoma of the head and neck regions.

STATUS OF THE PRIMARY TUMOR ON THE FIRST MEMORIAL HOSPITAL ADMISSION

Any institution designated as a collection center for a specific disease will receive many patients who have already been treated unsuccessfully elsewhere, as well as patients who have never undergone treatment. This is particularly true in the case of patients with melanoma, inasmuch as the results of failure are frequently so visibly spectacular and frightening to both patient and physician that care in such an institution is urgently sought. Previous inadequate treatment had been given to 60 per cent of the patients applying for treatment of melanoma at Memorial Hospital (Table II).

Possibly, no greater condemnation of medical practice exists than is presented by the large number of patients who are still being treated for melanoma by electrodesiccation and minimal surgical measures, when it is a known fact that the only sound treatment for this variety of cancer is adequate surgical removal of the primary growth and its regional lymphatics. It is possible, of course, that a certain number of patients with melanoma who never come to subsequent medical surveillance may unwittingly have been cured by electrodesiccation, but the failures are all too evident when advice is sought at an institution for the treatment of cancer. Since we do not know the cause of cancer, the traumatic implications of electrodesiccation cannot be accurately measured. The tragedy lies in both the patient's and his doctor's ignorance concerning the lethal potentiality of melanoma. Nowhere is this better illustrated than upon review of the clinical stage of the disease of these patients at the time of their first hospital admission. When the lesion was intact or only recently biopsied, 72 per cent were in Stage I, whereas only 29 per cent of those observed after prior electrodesiccation and 38 per cent after limited surgery were still in this most favorable stage of the disease (Table III). Obviously, this means that a correspondingly large number of patients is seen in Stage II, a still curable but far less favorable phase of melanoma. Finally, a proportionately larger group of patients had developed hopelessly incurable cancer after prior inadequate treatment or electrodesic-

TABLE II

STATUS OF PRIMARY LESION ON FIRST MEMORIAL HOSPITAL ADMISSION ACCORDING TO ANATOMIC LOCATION

	No. of Cases	Intact (Recent Biopsy)		Limited Excision		Electrodesiccation	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Head and Neck	137	44	32	78	57	15	11
Trunk	240	91	38	126	53	23	10
Extremities	537	231	43	262	49	44	8
Total	914	366	40	466	51	82	9

TABLE III

STATUS OF PRIMARY LESION ON FIRST MEMORIAL HOSPITAL ADMISSION ACCORDING TO STAGE OF DISEASE

	No. of Cases	Stage I		Stage II		Stage III	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Intact or Recent Biopsy	366	265	72	83	23	18	5
Previous Limited Excision	466	178	38	198	42	90	19
Previous Electrodesiccation	82	24	29	45	55	13	16
Total	914	467	51	326	36	121	13

cation, which is still being employed in the treatment of melanoma by those who are well trained and would vigorously oppose the use of such techniques for other varieties of cancer. Even though the disease is thus diagnosed, the patient's future has been so compromised by inadequate therapy that his chances of being in a favorable stage for definitive treatment are little better than 1 in 3.

STATUS OF THE PRIMARY LESION ACCORDING TO ANATOMIC LOCATION

A larger number of intact lesions was found in patients with melanoma of the extremities than in those with melanoma of the head and neck regions (Table II). It will be noted that only 40 per cent of these patients were previously untreated.

NUMBER OF PATIENTS WITH RECURRENCE OF MELANOMA AT THE TIME OF FIRST MEMORIAL HOSPITAL ADMISSION

Recurrence of melanoma had already developed in 27 per cent of patients having previously inadequate surgical excision and in 58 per cent of patients subjected to prior electrodesiccation. Of the entire series of 793 patients in Stages I and II, 143 or 18 per cent presented histologic evidence of recurrence upon the occasion of their first definitive treatment at Memorial Hospital.

By focusing our attention on the 193 patients with recurrence upon their first hospital admission, we observe that only 28 per cent were in Stage I, that 46 per cent were in Stage II and that 26 per cent were in Stage III (Table IV). Advanced stages of melanoma were more evident when the trunk and skin of the head and neck region were the site of the primary lesion. Only 143 or 74 per cent of those already recurrent on admission to Memorial Hospital, therefore, were suitable for definitive treatment, these 143 patients representing 18 per cent of the total of 793 patients in Stages I and II. Further discussion of local failure will be limited to the 793 patients in Stages I and II since they represent those

TABLE IV

STAGE OF DISEASE IN PATIENTS WITH LOCAL RECURRENCE ON FIRST MEMORIAL HOSPITAL ADMISSION

Anatomic Location	No. of Cases	Stage I		Stage II		Stage III	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Head and Neck	39	8	21	18	46	13	33
Trunk	48	9	19	24	50	15	31
Extremities	106	38	36	46	43	22	21
Total	193	55	28	88	46	50	26

for whom curative measures were still available at the time of their application for treatment (Table v).

LOCAL FAILURE

INADEQUATE TREATMENT AS A CAUSE OF LOCAL FAILURE

In assessing our inability to control the local manifestations of melanoma, there are several factors associated with faulty treatment methods which first come to mind. As already stated, some physicians still fail to suspect the possibility of cancerous change in moles and employ electrodesiccation as a quick and easy method for their eradication. Obviously, if treatment of a mole is indicated at all, such a nevus must be surgically excised and histologically identified.

Even when the possibility of melanoma is seriously considered, many surgeons, otherwise competently trained, fail to treat this tumor as a potentially lethal form of cancer. Inadequate excision, sometimes illogically combined with lymphatic dissection, continues to be the practice of many surgeons who are called upon to treat only occasional patients with melanoma.

Table V

STATUS OF PRIMARY LESION ON FIRST MEMORIAL HOSPITAL ADMISSION IN STAGE I AND II

	No. of Cases	Locally Recurrent	
		No.	Per Cent
Intact	348		
Previous Excision	376	103	27
Previous Electrodesiccation	69	40	58
Total	793	143	18

The location of the primary lesion may be partly responsible for the failure of surgeons to perform adequate excisional procedures. This is especially true when melanoma arises on the face where the proximity of such structures as nose, eyes, mouth or ears makes one hesitate to perform the extirpative surgery actually required for the control of this disease (Fig. 7, *A* and *B*). As can be amply illustrated, melanoma is just as malignant when arising from these structures as it is in other an-

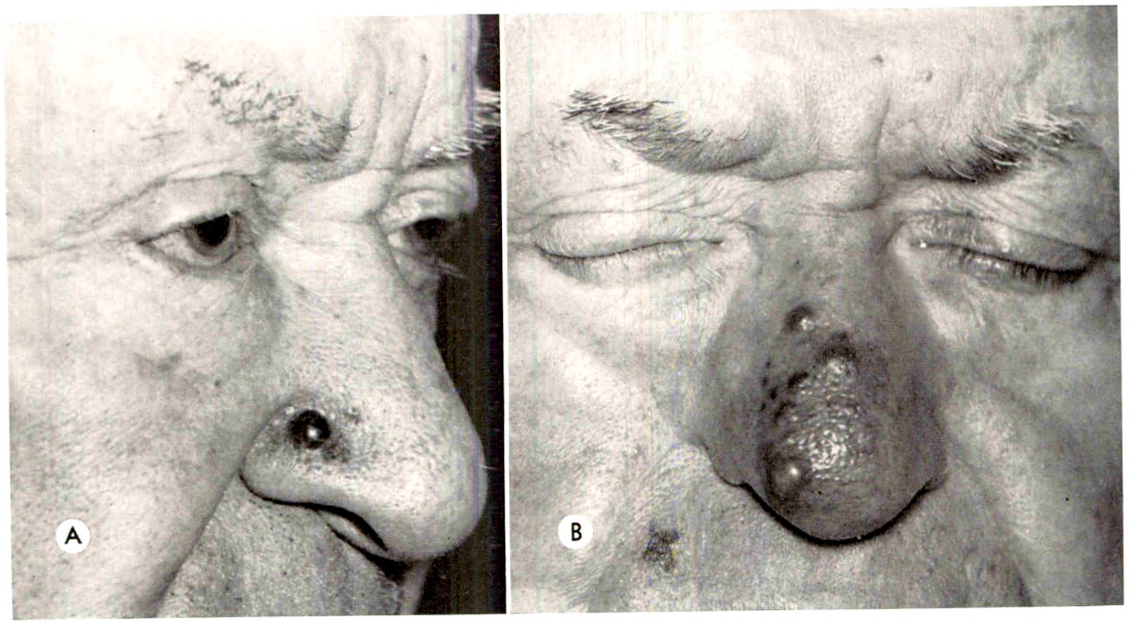


Fig. 7. (*A*) Untreated melanoma in skin of nose. (*B*) Multiple recurrences of melanoma 17 months following initial excision.

atomic sites. Similarly, there is a tendency to treat melanomas of the hands and feet by less vigorous methods than are applied elsewhere in the body. The recurrence rate after seemingly adequate operations for subungual melanoma is entirely too high to justify any operation less than ray amputation, disabling though it may be. Similar observations might be made regarding minimal excisions for melanoma of the foot.

Superficial melanoma occurs on the skin of the face, the trunk and extremities. Whether there is sound evidence or not at this time to treat this less invasive yet fully malignant variety of melanoma by means other than radical is seriously open to question.

It is obvious, therefore, that we must assess and re-assess our experience in any therapeutic endeavor in which the possibility of recurrence is ever present. The most effective treatment of curable melanoma is accomplished by surgical means, and, therefore, our re-assessment is primarily involved with the failures and success of surgery in controlling the local manifestations of this disease.

LOCAL FAILURE ACCORDING TO THE TYPE OF DEFINITIVE SURGERY AT MEMORIAL HOSPITAL

At this point, it becomes pertinent to discuss the definitive surgical techniques employed at Memorial Hospital during the 20 year period analyzed in this report. From 1935 to about 1945, the primary lesion was widely excised and the surgical defect repaired by sliding flaps or split thickness skin grafts. If the regional lymph nodes were adjacent to the primary lesion, they were removed in one continuous surgical procedure. When the primary tumor was located at too great a distance from the regional lymph nodes for such a procedure, the lymph node dissection was deferred for 2 to 4 weeks on the theory that this period of time was required for the "clearing" of the intervening lymphatics. This procedure was carried out regardless of the clinical impression of the status of the lymph nodes.

In the second period, 1945 to 1955, this general therapeutic policy was modified. In clinical Stage I melanoma, the primary site was widely excised and the defect grafted as in the preceding decade. *Simultaneous incontinuity dissection* of the regional lymph nodes was continued wherever this was anatomically possible, but otherwise lymphatic dissection was deferred until the lymph nodes became clinically palpable and suggestively metastatic. Although the need for high amputation under certain circumstances was suspected during this period, evidence was not presented to make this concept generally acceptable to the surgical staff charged with the care of the patients. Nevertheless, under certain circumstances, amputation or disarticulation associated with lymphatic dissection was occasionally performed. Of course, many patients never required lymphatic dissection although quite obviously it was impossible to determine at the onset who these fortunate persons might be. During these same years, if regional lymph nodes were deemed clinically positive for metastatic melanoma, a certain number of patients was treated by a wide surgical excision of the primary site in association with a *simultaneous and discontinuous* dissection of the regional lymph nodes. From time to time, patients were referred to this clinic for dissection of involved lymph nodes subsequent to local control of the melanoma by other surgeons some months or years previously. Simultaneous dissection of multiple (two) lymphatic node systems was sometimes performed when clinically indicated.

Since 1960, the principle of wide excision of the primary tumor associated with *elective* incontinuity or disseparate simultaneous lymphatic dissection has been carried out on the Mixed Tumor Service routinely. Sufficient time has not elapsed to estimate the actual values or dangers of this therapeutic approach. It is sufficient to say that the evidence thus far favors continuation of this policy. Wider experience has not supported the generally con-

ceived opinion that the incidence of local failure is thereby significantly increased (*i.e.*, by elective regional lymph node dissections).

Unfortunately, local failure was observed to a lesser or greater degree after all these operative measures (Table VI). Although the number of operations in each category is dissimilar, certain trends are quite readily demonstrable. After 793 operations for melanoma, local failure was manifested in 112 patients (14 per cent). The first observation of importance is that local failure was more than twice as frequent in Stage II (21 per cent) as in Stage I (9 per cent). Secondly, in Stage I the incidence of local failure was not significantly greater in patients subjected to the radical dissection of lymph nodes which were uninvolved than in those for whom only local removal of the primary tumor was performed. Although, local recurrence appeared less frequently after the so-called incontinuity techniques, the incidence of local failure after this seemingly ideal operation for melanoma was nevertheless found to be 9 per cent in Stage I and 19 per cent in Stage II. The *discontinuous*, *disseparate* simultaneous or deferred procedures were followed by a greater recorded incidence of local failure: 13 per cent in Stage I and 27 per cent in Stage II. This is a very serious complication in the history of the patient with melanoma and it has been mainly responsible for prompting the development of techniques employing whole limb perfusion with chemotherapeutic agents.[10] The idea is undoubtedly sound but the efficacy of the drugs presently available in our therapeutic armamentarium is under serious question.

The third and final observation of importance was that of the incidence of local failure after the performance of major amputations or disarticulations. When it is realized that such procedures were, at that time, performed out of desperation, a local failure rate of 6 per cent in Stage I and 22 per cent in Stage II is acceptable, particularly when compared with the aforementioned local recurrence rate after disseparate lymph node dissections. As might be anticipated, however, 7 out of the 8 recurrences developed after amputations for melanoma in Stage II.

LOCAL FAILURE AFTER DEFINITIVE SURGICAL TREATMENT FOR MELANOMA ARISING IN VARIOUS ANATOMIC SITES

A. *Cutaneous Melanoma of the Head and Neck Regions.* The incidence of local failure after operations for patients with melanoma of the head and neck was 15 per cent in Stage I and 45 per cent in Stage II (Table VII). The high incidence of local failure

TABLE VI

FREQUENCY OF RECURRENCE AND LOCAL METASTASIS AFTER MEMORIAL HOSPITAL TREATMENT
ALL ANATOMIC SITES

	Stage I				Stage II			
	No. of Cases	No. of Recurrences	No. of Metastases	Per Cent	No. of Cases	No. of Recurrences	No. of Metastases	Per Cent
Excision	256	16	5	8				
Excision and:								
Disseparate Lymph Node Dissection	79	5	5	13	101	13	14	27
Incontinuity Lymph Node Dissection	116	6	4	9	193	20	16	19
Amputation	16	—	1	6	32	5	2	22
Total	467	42		9	326	70		21

Table VII

FREQUENCY OF RECURRENCE AND LOCAL METASTASES AFTER MEMORIAL HOSPITAL TREATMENT
MELANOMA OF THE HEAD AND NECK

	Stage I				Stage II			
	No. of Cases	Recurrences	Metastases	Per Cent	No. of Cases	Recurrences	Metastases	Per Cent
Excision	42	9		21				
Excision and Lymph Node Dissection	25	1		4	38	17		45
Total	67	10		15	38	17		45

Table VIII

FREQUENCY OF RECURRENCE AND LOCAL METASTASES AFTER MEMORIAL HOSPITAL TREATMENT
MELANOMA OF THE TRUNK

	Stage I				Stage II			
	No. of Cases	Recurrences	Metastases	Per Cent	No. of Cases	Recurrences	Metastases	Per Cent
Excision	44	–	–					
Excision and Lymph Node Dissection	59	4	4	14	99	4	10	14
Total	103	8		8	99	14		14

after incontinuity lymph node dissections in Stage II is observed. These data were obtained from the charts of 105 patients who were followed over 5 years or to their earlier fatal termination.* The anatomic structures of the head and neck regions are so closely approximated and constantly visible that generous excisions of normal adjacent tissue to the primary tumor frequently were not carried out for fear of mutilation. Operative procedures designed for the cure of other varieties of cancer in these same regions were daily performed without an apparently comparable concern for the external appearance of the patient. The same attitude toward the eradication of cutaneous melanoma of the head and neck regions is strongly recommended. Obviously, a 21 per cent recurrence rate after a "wide" excision for melanoma would indicate that the operation had not been wide enough.

B. *Melanoma of the Trunk.* As might have been anticipated, local failure was not so serious a problem for patients with melanoma of the trunk because large incisions thus located are neither obviously so deforming nor so readily visible as in other anatomic sites (Table VIII). For this reason, perhaps, there was no incidence of recurrence following wide excision alone, yet the local failure rate after wide excision with lymph node dissection was greater in Stage II (14 per cent) than in Stage I (8 per cent).

C. *Melanoma of the Extremities.* Mention has already been made of the surprisingly high local failure rate after amputations. Inasmuch as there is considerable controversy regarding the indications for whole limb perfusion with alkylating agents for patients with melanoma of the extremities,

* Dr. E. L. Frazell and the Staff of the Head and Neck Service at Memorial Hospital kindly permitted inclusion of these data obtained from their patients.

TABLE IX

FREQUENCY OF RECURRENCE AND LOCAL METASTASIS AFTER MEMORIAL HOSPITAL TREATMENT MELANOMA OF THE EXTREMITIES

	Stage I				Stage II			
	No. of Cases	Recurrences	Metastases	Per Cent	No. of Cases	Recurrences	Metastases	Per Cent
Excision	170	7	5	7				
Excision and Disseparate Lymph Node Dissection				13				24
Deferred	50	5	1	12	56	7	6	23
Simultaneous	19	0	3	16	22	2	4	27
Excision and Incontinuity Lymph Node Dissection	42	1	1	5	79	3	10	16
Amputation	16	0	1	6	32	5	2	22
Total	297	13	11	8	189	17	22	21

it behooves us to consider here the problem of local failure in melanoma of the extremities in greater detail. In our 486 operations for melanoma of the extremities carried out over 20 years, subjected to a recapitulation period of over 10 years, there has been a local failure rate of 8 per cent in Stage I and 21 per cent in Stage II (Table IX).

According to our data, there is a distinctly greater hazard of local failure for patients with melanoma of the *lower* extremity in Stage I (10 per cent of 197 patients) than for those of the *upper* extremity in a comparable stage of the disease (4 per cent of 100 patients) (Table X). Vulnerability for the patients in Stage II is the same (21 per cent) for both upper and lower extremity.

Inasmuch as the greater problem relating to local failure arises in patients with melanoma originating in the skin of the extremities *below* rather than *above* the knees and elbows, we have subdivided our material accordingly.

By so doing we observe that the danger of local recurrence for 76 patients with Stage I melanoma above the knees or elbows was 3 per cent, whereas for 221 patients with similar cancers located distal to the knees and elbows it was 10 per cent (Tables XI and XII). The incidence of local failure in Stage II is roughly the same

TABLE X

LOCAL FAILURE AFTER MEMORIAL HOSPITAL TREATMENT IN MELANOMA OF THE EXTREMITIES ACCORDING TO ANATOMIC LOCATION

	Stage I			Stage II		
	No. of Cases	No.	Per Cent	No. of Cases	No.	Per Cent
Above Elbow	45	1	2	32	7	22
Below Elbow	55	3	5 } 4%	80	16	20 } 21%
Above Knee	31	1	3	59	12	20
Below Knee	166	19	11 } 10%	18	4	22 } 21%
Total	297	24	8	189	39	21

TABLE XI

LOCAL FAILURE AFTER MEMORIAL HOSPITAL TREATMENT IN MELANOMA OF THE EXTREMITIES ABOVE ELBOW AND KNEE

	Stage I				Stage II			
	No. of Cases	Recurrences	Metastases	Per Cent	No. of Cases	Recurrences	Metastases	Per Cent
Excision	30	0	0	0				
Excision and Disseparate Lymph Node Dissection				0				12
Deferred	5	0	0	0	11	0	2	18
Simultaneous	3	0	0	0	6	0	0	0
Excision and Incontinuity Lymph Node Dissection	37	1	1	5	66	2	10	18
Amputation	1	0	0	0	8	5	0	63
Total	76	1	1	3	91	7	12	21

throughout both upper and lower extremity.

1. Melanoma Arising above the Elbows and Knees. In Stage I the most striking observation was the development of recurrence after the incontinuity operation more often than after discontinuous techniques. In the presence of lymphatic metastasis (Stage II), this unexpected disparity is again observed. In fact, there is a reversal of the anticipated incidence; *i.e.*, 18 per cent after incontinuity dissections as opposed to 12 per cent for the disseparate removal of lymph nodes. The *most striking* feature noted in Table XI is the high incidence of recurrence after high amputation and lymph node dissection for melanoma in Stage II located proximal to the knee and elbow in 5 of 8 patients (63 per cent). Although the number of cases is small, the warning is clear. Amputations for melanoma of the extremities in Stage II *proximal* to the elbows and knees must be recommended only after a very careful physical and roentgen examination, and probably never if the lymph nodes proximal

TABLE XII

LOCAL FAILURE AFTER MEMORIAL HOSPITAL TREATMENT IN MELANOMA OF THE EXTREMITIES BELOW ELBOW AND KNEE

	Stage I				Stage II			
	No. of Cases	Recurrences	Metastases	Per Cent	No. of Cases	Recurrences	Metastases	Per Cent
Excision	140	7	5	9				
Excision and Disseparate Lymph Node Dissection				15				28
Deferred	45	5	1		45	7	4	
Simultaneous	16	0	3		16	2	4	
Excision and Incontinuity Lymph Node Dissection	5	0	0	0	13	1	0	8
Amputation	15	0	1	7	24	0	2	9
Total	221	12	10	10	98	10	10	20

to the inguinal ligament contain metastasis. Indeed, a laparotomy should be carried out prior to the intended amputation for melanoma of the lower extremity and, if intra-abdominal metastases are present, amputation is contraindicated.

2. Melanoma Arising below the Elbows and Knees. The higher incidence of local failure and especially of intervening or "in-transit" metastasis when a major joint separates the primary site from regional lymphatic drainage areas has already been mentioned. This has occurred not infrequently after wide excisional procedures alone (9 per cent) for Stage I melanoma. The anatomic difficulty of performing incontinuity operations in this anatomic setting has required greater use of the discontinuous techniques. There occurs a distinct increase in the local failure after this operation (15 per cent). In Stage II the development of local recurrence and intervening metastasis is especially prone to occur after disseparate lymph node dissection whether the operation be simultaneous or deferred. There is absolutely no support for the concept of staging the removal of primary lesion and the regional lymph nodes when the latter are clinically and histologically positive. Hence, the concept of high amputation and lymphatic dissection for clinical Stage II melanoma located *below* the knees or elbows is strongly supported by the low incidence of local failure (9 per cent) as compared with the same operative technique for patients with the primary lesion arising above elbows and knees (63 per cent).

Review of these data gives further support to the previously expressed observation that local failure, especially as intervening metastasis, is an unfortunate complication after operations for Stage II melanoma of either the upper or lower extremity. It occurs somewhat more frequently after discontinuous than incontinuity dissections for lymph nodes containing metastatic cancer and is especially disconcerting when it occurs subsequent to major amputation of an extremity.

Table XIII

LOCAL FAILURE AFTER MEMORIAL HOSPITAL TREATMENT ALL ANATOMIC SITES

	Stage I		Stage II	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Head and Neck	67	15	38	45
Trunk	103	8	99	14
Extremities	297	8	189	21
Total	467	9	326	21

SUMMATION OF THE FACTORS RELATING DEFINITIVE SURGICAL TECHNIQUES TO THE FREQUENCY OF LOCAL RECURRENCE

Local failure occurs after the definitive treatment of melanoma in all anatomic sites (Table XIII), whatever technique was employed in both curable stages of the disease (Table VI). The more ominous feature of intervening and locally disseminating metastasis complicates the problem almost as often as does recurrence of cancer in the operative site. Local failure occurs in over 20 per cent of patients in Stage II, regardless of the operative procedure employed, even after high amputation or disarticulation (22 per cent) (Table VI). Possibly, the wider application of amputative techniques for Stage II melanoma originating distal to the knees and elbows may not only be effective in reducing the frequency of local failures but be life saving as well.

STATUS OF THE LESION ON FIRST MEMORIAL HOSPITAL ADMISSION RELATED TO LOCAL FAILURE SUBSEQUENT TO DEFINITIVE TREATMENT

In attempting to relate the development of local failure after definitive treatment to the original status of the primary lesion on the occasion of the first Memorial Hospital admission, several interesting observations may be made (Table XIV). Previous inadequate treatment favors the possibility of future local failure, particularly when such manifestations have appeared

TABLE XIV

LOCAL FAILURE AFTER MEMORIAL HOSPITAL TREATMENT
STATUS OF PRIMARY LESION ON FIRST MEMORIAL HOSPITAL ADMISSION

	Stage I		Stage II	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Intact or Recent Biopsy	265	10	83	28
Previous Limited Treatment without Local Recurrence	147	5	155	15
Previous Limited Treatment with Local Recurrence	55	15	88	26

prior to definitive treatment. If one recalls the high proportionate frequency of patients with melanoma in advanced stages, and hence the high ultimate mortality occurring in patients who have had inadequate treatment prior to definitive surgery, it becomes clear that such incomplete methods have been successful only in the occasional case in which the disease has continued to remain localized.

TREATMENT OF MELANOMA LOCALLY RECURRENT AFTER DEFINITIVE SURGERY

A. *Cutaneous Melanoma of the Head and Neck.* The treatment of locally recurrent melanoma in these regions after primary definitive surgery would seem to pose an almost impossible problem. Irradiation proved totally inadequate in offering even minimal local control of melanoma. Re-excision with or without skin grafting and radical neck dissection were carried out in the majority of instances. For melanoma of the cheek and temple, superficial parotidectomy was also performed. The fact that radical surgery was still possible in this group of patients indicates the inadequacy of what was considered definitive treatment primarily. More than anything else, this observation indicates the need for carefully planned definitive surgery at the time of initial diagnosis as the primary means of preventing recurrence.

B. *Melanoma of the Trunk.* The treatment of locally recurring melanoma of the trunk after primary definitive surgery is, for obvious anatomic reasons, merely wide re-excision. Incontinuity regional lymph node dissections, if not a part of the original surgical endeavor, should clearly be performed. Inability to anticipate the probable area of lymph node metastasis at the time of primary definitive surgery sometimes occurs, particularly with midline lesions. The location of recurrence in such instances, if it develops at all, may indicate the direction of lymphatic spread.

C. *Melanoma of the Extremities.* If the lesion is solitary and within 10 cm. of the primary site, a second wide excision and plastic repair is the procedure of choice. If recurrence or metastases are multiple and distal to a major joint separating primary site (*i.e.*, elbow, knee) from the regional lymphatic drainage area, amputation at the highest proximal joint is strongly advocated. Such a recommendation implies a rigid search, including laparotomy, for other evidence of metastasis before resorting to major exarticulation.

END RESULTS IN THE TREATMENT OF LOCAL FAILURE AFTER DEFINITIVE SURGERY

Once local failure develops after definitive treatment for melanoma, the prognosis, while not hopeless, is grave. Within 6 months, 38 per cent of the recurrences will have become manifest and at the end of 2 years, 79 per cent (Fig. 8). A most striking observation is that those patients who develop evidence of local failure within 6 months of definitive surgery have little chance of 5 year survival. When the interval between primary treatment and local

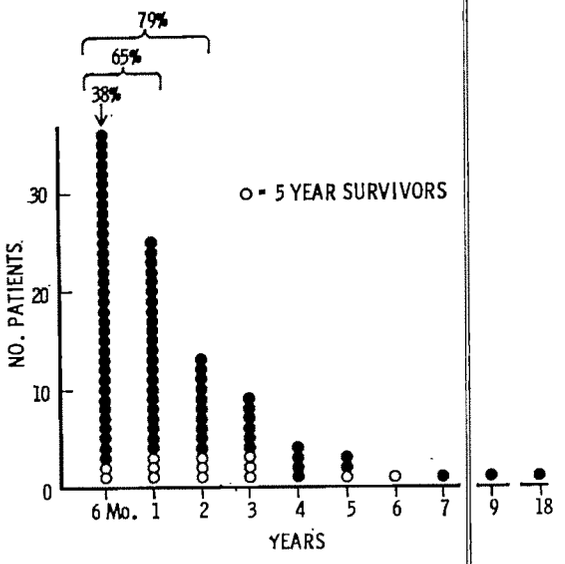


FIG. 8. Incidence of local failure as related to time of appearance following definitive treatment for melanoma.

failure is prolonged, the permanent outlook is improved. However, the occasional late recurrence of melanoma, even up to 18 years after treatment, emphasizes the necessity for prolonged follow-up examinations.

Suitable data for 5 year survival estimates were available in 94 patients (Table XV). The 5 year survival rate was 15 per cent. If one excludes the 30 patients who had developed metastatic melanoma to such an extent as to preclude any treatment, 13 of 64 or 20 per cent attained clinical cure.

In summary, the number of patients is small for whom effective treatment can be offered for local recurrence of melanoma following primary definitive surgery. We have not observed any striking superiority of amputation over excisional surgery in achieving ultimate cure but believe that it should be employed for locally recurrent melanoma below the elbow or knee. Longevity can rarely be achieved by any method of treatment when multiple recurrences appear above the elbow or knee.

TABLE XV

RESULTS FOLLOWING TREATMENT FOR LOCAL FAILURE

	No. of Cases	No Evidence of Disease at 5 Years	
Untreated	30	0	
Excision	47	10	
Excision and Lymph Node Dissection	7	1	
Amputation	10	2	
Total Treated	64	13	20%
Total No. of Cases	94	13	15%

FACTORS AFFECTING THE 5 YEAR CANCER FREE SURVIVAL RATE

The status of the primary lesion on the first hospital admission appears to present little bearing on ultimate survival (Table XVI). In excess of 70 per cent of patients in Stage I remained cancer free regardless of this factor, whereas the anticipated impact of lymphatic metastasis was felt by

TABLE XVI

FIVE YEAR SURVIVAL AFTER MEMORIAL HOSPITAL TREATMENT
STATUS OF PRIMARY LESION ON FIRST MEMORIAL HOSPITAL ADMISSION

	Stage I		Stage II	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Intact	240	74	81	22
Previous Limited Treatment without Local Recurrence	137	73	146	24
Previous Limited Treatment with Local Recurrence	52	67	86	27

all patients in Stage II in whom 5 year survival was attained in about 24 per cent of cases only.

Other factors which may influence the outcome for the patient with locally metastatic or recurring melanoma include the following: the location of the recurrence; the number of recurrent or metastatic nodules; the distance of the local metastasis from the primary site; the presence or absence of metastasis in the regional lymph nodes and the method of treatment.

In a previous communication[11] we noted that when a solitary recurrence appeared within the surgical scar or immediately adjacent to it, 13 of 31 patients attained a 5 year cancer free survival by adequate treatment. When local metastasis developed at a distance of 5 or more centimeters from the primary site, only a few patients did attain longevity. Multiplicity of locally metastatic or recurrent tumor greatly diminished the possibility of 5 year cancer free survival regardless of their relation in space to the primary site. Although a few patients have been known to live for many years after more than one experience with local failure, such occurrences are encountered infrequently.

The effect of metastasis to lymph nodes on the patient with locally recurrent melanoma is extremely grave. The combination of both factors, while not producing a hopeless clinical setting, is seldom followed by a successful conclusion.

FACTORS PREDISPOSING TO LOCAL FAILURE

The presence of metastatic melanoma in the regional lymph nodes is possibly the single most readily demonstrable factor in the problem of local recurrence and/or intervening metastasis. When numerous lymph nodes are so involved, the filtration process becomes less efficient, the intervening lymph vessels become dilated, and entrapped melanoma cells may either pass through their walls or aggregate within their lumina. Because we have observed the high incidence of regional lymph node involvement in by far the majority of patients demonstrating wound or intervening recurrence from melanoma of the extremities and from melanoma of the head and neck, we are forced to relate these two factors in the life history of this disease. If distance of the primary site of melanoma from the regional lymph node area were a significant factor predisposing to local recurrence, then one would anticipate a higher incidence of local failure in the lower extremity than in the head and neck area. Our data do not support this assumption.

PREVENTION OF LOCAL FAILURE

Inasmuch as it has been established that local recurrence develops considerably more often after adequate operations for Stage II than for Stage I melanoma, it is obvious that no surgical technique will ever supplant earlier diagnosis. Nevertheless, more adequate local removal of the primary tumor for patients in Stage I must be the basic tenet of our therapeutic approach to this disease. Only rarely may this truly be accomplished without the employment of plastic procedures such as skin grafting, rotation of flaps, Z plasty, etc. No less than 5 cm. of normal skin, subcutaneous fat and fascia, circumferentially surrounding the primary tumor, must be included in the surgical specimen. For melanoma of the trunk and extremities, we recommend excision of a strip of tissue proximal to the tumor for a distance of at least 10–15 cm.

Far wider sacrifices of skin and subcutaneous tissues must be accepted by patient and surgeon alike if the local recurrence and ultimate cure rate is to be improved for melanoma of the head and neck. After standard excisional surgery for melanoma at Memorial Hospital, local recurrence was considerably higher where the primary tumor involved the face than for any other anatomic site. Adequate surgical excision for melanoma of the eyelids and adjacent skin, the nose, and the ear will always remain a difficult problem because of obvious cosmetic considerations.

MANAGEMENT OF THE REGIONAL LYMPH NODES

Wherever possible, en bloc dissection of the primary growth and its regional lymph nodes is recommended. In this clinical setting, local recurrence and/or intervening metastasis occurs less frequently even when the lymph nodes contain a solitary metastasis. Inasmuch as removal of regional lymph nodes is a basic tenet in all cancer surgery, such dissections are recommended when the lymph nodes are clinically negative even though a mono-bloc dissection cannot be performed. When lymph node metastasis was not suspected clinically, the 5 year survival rate has been in excess of 50 per cent even when metastasis was subsequently discovered histologically.[6]

If the primary tumor is uncontrolled and the regional lymph nodes are clinically and histologically positive and if a mono-bloc technique cannot be carried out because of the distance separating the primary lesion and the regional drainage system, it is our belief that forequarter of hip joint disarticulation is mandatory. In this clinical setting, the 5 year survival rate is low and the possibility of recurrence and metastasis within the extremity is high. With proper selection and careful examination of patients, it has been shown that after these major amputations and exarticulations for melanoma a 5 year cancer free survival has been offered nevertheless to a certain number of these patients.[8]

SUMMARY AND CONCLUSIONS

1. Inadequate treatment of melanoma delays definitive management and increases the hazard of dissemination to regional lymph nodes and distant organs.

2. Adequate treatment of melanoma is followed by local failure in 9 per cent of patients in Stage I, 21 per cent in Stage II.

3. Increased occurrence of local failure associated with melanoma of head and neck, fingers and soles of feet is probably due to inadequate excision.

4. Local failure is more commonly observed after treatment of melanoma below than above the elbows and knees.

5. Local failure occurs all too frequently after amputation for Stage II melanoma located proximal to the knees and elbows.

6. Local failure occurs more commonly after disseparate than incontinuity lymph node dissections in Stage II, but the difference is not remarkable.

7. There is no basis for performing deferred as opposed to simultaneous discontinuous lymph node dissections as far as the rate of local failure is concerned.

8. Seventy-nine per cent of local failures occur within the first 2 years of definitive surgery and among these cases mortality is high. When local failure occurs after 2 years, the opportunity for long term survival is enhanced.

9. It may be possible to decrease the incidence of local failure by more adequate primary surgical treatment, but the most promising preventative of local failure is early recognition of melanoma and prompt surgical resection before lymphatic metastasis will have occurred.

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MUCOSAL MELANOMAS OF THE HEAD AND NECK*

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IN A recent review of the Memorial Center records of all patients afflicted with melanomas of the head and neck area during the 12 years 1947 through 1958, the following anatomic distribution was noted:

Skin of head and neck	179 patients
Mucosa of mouth, upper respiratory tract and orbit	43 patients
Metastatic cervical lymph nodes with no primary lesion found	6 patients
Total	228 patients

It is the purpose of the author to give a factual account of the 43 patients with mucosal melanomas who were examined and, for the most part treated, at Memorial Center during this period. Fortunately, this variety of cancer is rare; it is highly lethal and carries a much poorer prognosis than the more common cutaneous melanoma. In a 1955 report from this clinic on 26 patients with mucosal melanomas, only 1 patient was listed as having survived free of cancer for more than 5 years.[7] Our more recent experience with these tumors has shown some improvement in our 5 year salvage rate. Although our present group of patients is almost twice as large, there is no indication that the diagnosis was made sooner or that the surgery was more aggressive than reported in the 1955 study.

CLINICAL MATERIAL

Of the 43 patients, there were 28 men and 15 women, a preponderance of almost 2 to 1. A similar sex distribution was noted also in cases of cutaneous melanomas from this center.[3] Forty patients were white, 2 were Negroes and 1 was Puerto Rican. Melanoma is a cancer which favors the white race. In Negroes melanomas are usually found in the mucous membrane of the mouth and eye, skin of the lower extremity and skin of the head and face.[8]

Unlike the more common forms of epidermoid carcinoma of the head and neck, mucosal melanoma tended to occur in somewhat younger age groups. From Figure 1, it can be seen that two-thirds of our patients were in the fourth to sixth decade of life.

AGE DISTRIBUTION

The youngest patient was a 4 year old Negro boy. He had a 4 cm. melanoma in the left buccal mucosa which grew rapidly and failed to respond to radiation and chemotherapy. He also had an adenocarcinoma of the left adrenal gland. He was dead of disseminated melanoma in 7 months.

The oldest patient was a 79 year old white man who came to Memorial Center following resection of a melanoma on the mucosa of the nasal septum. The primary cancer apparently was controlled by this first operation. During the next 4 years, 5 additional deposits of metastatic melanoma

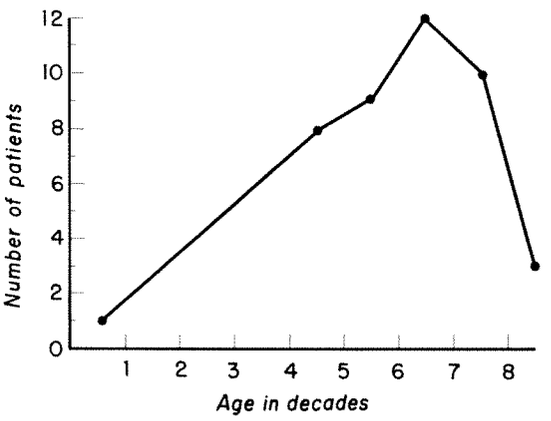


FIG. 1. Age incidence of 43 patients with mucosal melanomas.

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
From the Head and Neck Service, Memorial Center, New York, New York.

were excised from the soft tissue of the left cheek at Memorial Center. Six and one-half years following our first operation, he was clinically free of melanoma. He died suddenly of a heart attack while mountain climbing at 85 years of age.

Except for a tendency to be younger, the 43 melanoma patients were in other respects similar to the general group of cancer patients treated at our Center.

HISTOPATHOLOGY AND GROSS APPEARANCE

In each case, the diagnosis of melanocarcinoma was confirmed by histologic examination in the pathology department. There is a tendency for error in the diagnosis of melanoma which led us to insist on confirmation by one or more of our own pathologists. Although it has been suggested that mucosal melanomas appear more anaplastic under the microscope than do the cutaneous variety,[1] such a distinction was not mentioned in the reports of these 43 patients.

Thirteen of the mucosal melanomas were black or dark brown in color. Nineteen of the tumors were pink and 5 were essentially colorless; 6 could not be classified due to previous treatment (usually excision) elsewhere.

In the pigmented tumors, the diagnosis of melanoma was easy to suspect clinically. Twenty-six of the tumors were ulcerated on first examination. Those which were pink had a somewhat fleshy appearance and tended to be softer and less infiltrative than squamous cancers. In contrast to cases of cutaneous melanomas, none of our 43 patients showed evidence of satellite formation around the primary mucosal tumor. An exception to this experience is shown in Figure 6, a recent case of melanoma of the larynx which is not included in the present series.

DURATION FROM FIRST SYMPTOM, PREVIOUS TREATMENT AND SIZE OF MELANOMA ON ADMISSION

The time interval between the first symptoms and the institution of treatment in our patients tended to be unduly long. The absence of early pain was probably a contributing factor causing delay. Only 9 patients sought medical advice during the first 6 months of their illness. Eight patients waited 6 months to 1 year, 17 patients waited 1 to 2 years and 8 patients 2 to 5 years. One 47 year old man noted a small slowly growing brown tumor in the mucosa of his lower lip for a period of over 10 years before he sought medical aid. A generous excision of this true melanoma resulted in a salvage of over 10 years to date. Biologically, this tumor has certainly been quiescent and nonaggressive.

Only 4 patients were referred to us without having had previous treatment. Thirty-eight patients (88 per cent of the entire group) underwent some type of local resection of the primary melanoma, usually for diagnostic purposes. When the diagnosis of melanoma was obtained, many of these patients were promptly sent to us for further advice and management, even though the local excision of the tumor was judged adequate by the referring surgeon. Fourteen of the patients had more than one surgical procedure (usually excisional biopsy followed by a wider resection) before referral to us.

Only 1 patient, a 72 year old man with a 2 cm. melanoma in the right nasal cavity received previous radiation therapy, from which no benefit was noted. A subtotal resection of the right maxilla including exenteration of the right orbit was carried out at Memorial Center. He was clinically free of melanoma 2 months later, when he died suddenly from pulmonary embolism.

The size of the primary melanoma was not recorded in 5 patients and in 1 patient there was no tumor palpable after previous local excision. In 14 patients the tumor was less than 2 cm. in size; this group suggests early diagnosis and half of them were salvaged for 5 years or longer. Nineteen melanomas were 3 to 5 cm. in size. In 4 patients, the presenting melanoma was larger than 5 cm.; all of these patients died of their disease.

TABLE I

ANATOMIC DISTRIBUTION OF 43 CASES OF MUCOSAL MELANOMAS

Anatomic Location	No. of Patients	NED 5 years
Nasal cavity	13	4
Paranasal sinuses	9	1
Antrum 6		
Ethmoid 2		
Frontal 1		
Buccal mucosa	5	
Lips	4	2
Lower 3		
Upper 1		
Gum	3	
Hard palate	2	
Larynx (extrinsic)	2	1
Eye (conjunctival)	2	2
Tonsil	1	
Tongue	1	1
Floor of mouth	1	
Total	43	11

NED = No evidence of disease.

PRIMARY SITES OF THE MUCOSAL MELANOMAS

The anatomic distribution of the 43 melanomas is listed in Table 1. The number of salvaged patients for each anatomic site is also given in this table. The 2 melanomas of the eye originated on the bulbar conjuctiva. In Figure 2, *A*, *B* and *C* a similar case is shown. Melanomas arising along the uveal tract of the eye are considered to be an entirely different kind of cancer and, therefore, none was included in the present study which was limited to mucosal tumors.

It is interesting to note that there were more successfully treated cases in the nasal cavity group than in any other anatomic site. This finding is probably due to the fact that the nose is also the commonest site for melanoma, since the nasal cavity

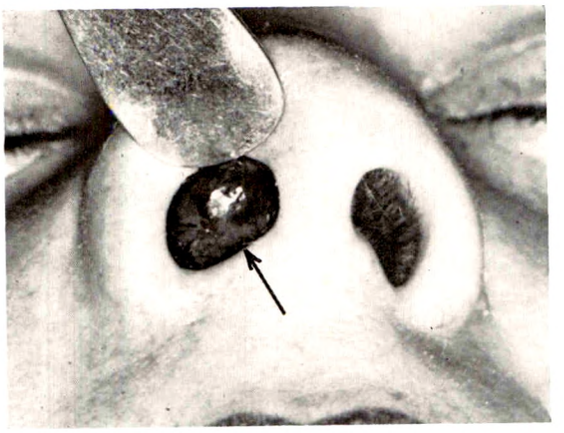


FIG. 3. A pink amelanotic melanoma filling the right nasal cavity. This 42 year old woman was our only patient to undergo an elective neck dissection. See text.

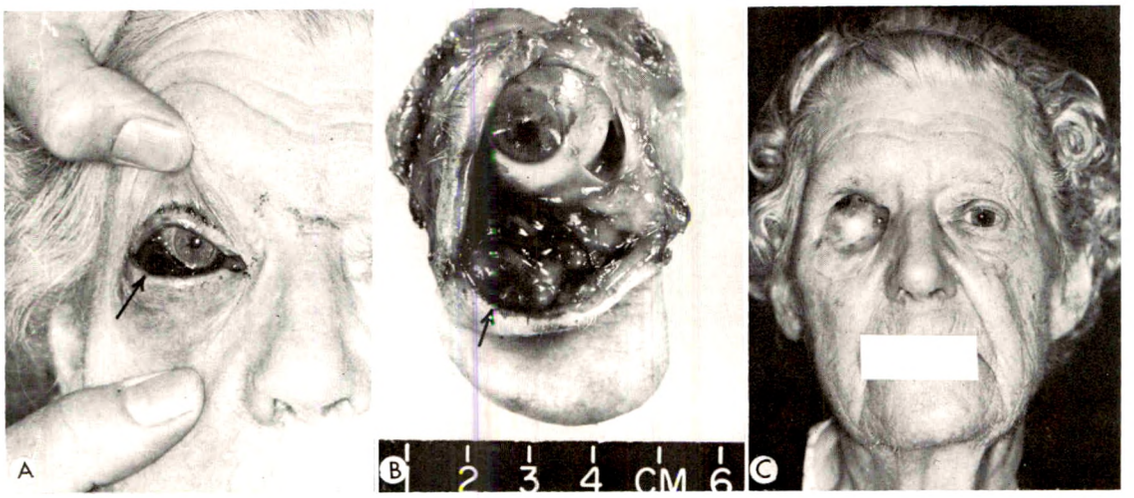


FIG. 2. (*A*) Arrow points to melanoma in mucosa of right lower eyelid. (*B*) Operative specimen. Contents of right orbit. (*C*) Appearance of this 76 year old patient 3 months postoperation. The right orbital defect is covered with a split-thickness skin graft.

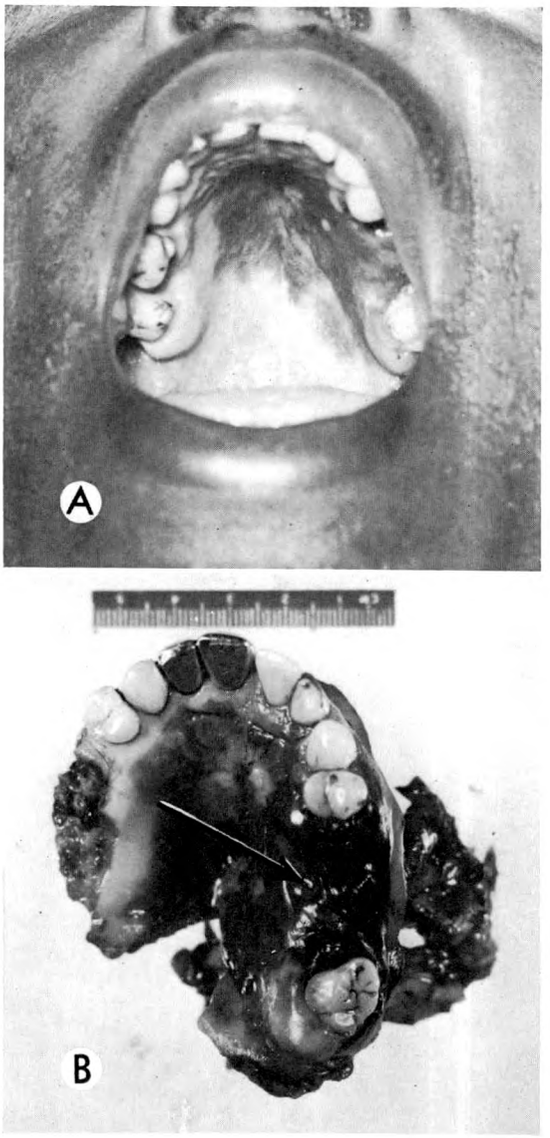


Fig. 4. (*A*) A melanoma of the mucosa of the hard palate in a 42 year old Negro. (*B*) Operative specimen. This patient was dead in 44 months of locally recurrent melanoma plus regional and distant metastases.

does not lend itself well to either the early diagnosis or wide resection of a melanoma. Occasionally, the tumor can be easily seen at the external nares as demonstrated in Figure 3.

In Figures 4, *A* and *B*; and 5, melanomas arising within the mouth are demonstrated, and Figure 6 shows a melanoma of the extrinsic larnyx. All 3 of these tumors contained black pigment which made the clinical diagnosis of melanoma highly probable.

Stage of Disease on Admission and Other Factors Relating to Prognosis

The stage of disease on admission is tabulated in Table II; in the right hand column are listed the 11 patients who had no evidence of disease at 5 years. All cases were staged into only 3 groups; it has been our experience that further subgrouping, based usually on clinical appraisal, leads only to confusion.

Surprisingly, most of the successfully treated cases were not those in Stage I, where the melanoma remained localized to the primary tumor. Six patients with regional lymph node metastases were salvaged for 5 years or longer. Four patients with distant metastases were all dead of melanoma from 2 to 7 months.

Of the 11 patients with no evidence of disease at 5 years, 8 were males and 3 were females. Based on so few patients, this preponderance of men is probably not significant. Only one pregnancy occurred among the 15 women in the entire group. A 31 year old patient became pregnant 6 months following partial resection of the right maxilla for a melanoma of the upper

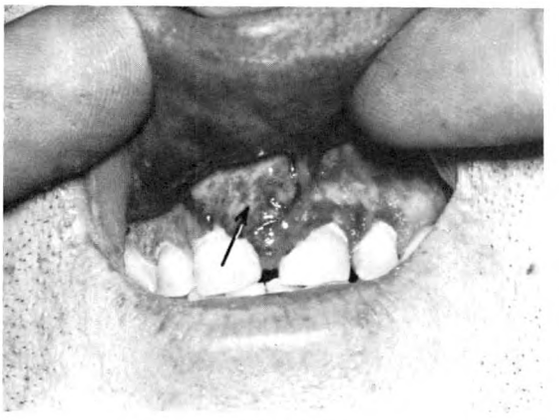


Fig. 5. A melanoma of the right upper gum in a 39 year old man. A partial resection of the right maxilla with tracheostomy was made. This patient had no evidence of disease in the mouth but died 8 months later of distant metastases.

gum and 1 month after a right neck dissection for metastatic lymph nodes. Six weeks after delivery of a normal girl, she died of melanoma of unknown extent. No conclusions can be made from this solitary case.

Seven of the successfully treated patients had biopsies only before referral, 1 patient had no previous treatment and 3 patients had inadequate local excisions. This experience suggests that early definitive treatment is the most effective. Also in 7 of the 11 successfully treated patients, the primary melanoma was less than 2 cm. in size. This observation seems important and indicates the value of early diagnosis and treatment. Only 1 of these patients presented a melanoma larger than 3 cm.

Five of the successfully treated melanomas showed ulceration and 6 did not. This finding is hard to evaluate and is probably not significant due to frequent previous biopsies which undoubtedly produced ulceration in some intact tumors. As was noted earlier, none of the 43 mucosal melanomas showed any satellite formation.

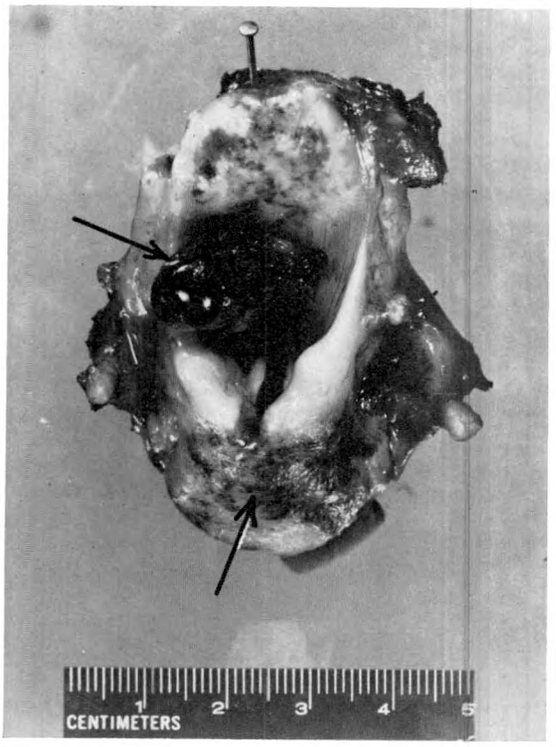


Fig. 6. Operative specimen of a larynx of an 86 year old woman. The upper arrow indicates the primary melanoma at the left base of the epiglottis. The lower arrow points to pigmented satellites in the postcricoid mucosa.

Table II

STAGE OF DISEASE ON ADMISSION OF 43 CASES OF MUCOSAL MELANOMAS

Stage of Disease on Admission	No. of Patients	NED 5 Years
1. Localized	31	5
2. With neck lymph node metastases	8	6
3. With distant metastases (generalized disease)	4	0
Total	43	11

NED = No evidence of disease.

TREATMENT

Most of the 43 patients were treated with surgery. Radiation therapy was used in those few patients who refused operation or in the occasional nonresectable cases. Forty patients were treated on the Head and Neck Service. A 4 year old boy was treated on the Pediatric Service. One melanoma of the lower gum and 1 melanoma of the extrinsic larynx were operated on by other surgical services.

Radiation therapy, sometimes supplemented with radium needles or radon seeds, did not prove to be effective in controlling melanoma. Eleven of 12 patients in whom it was used, died of melanoma from 5 to 37 months after treatment. The remaining patient received a large dose of radiation therapy to a melanoma in the right nasal cavity. When the tumor failed to regress, she was referred to us for resection of the right maxilla, including orbital exenteration. She died 2 months later of pulmonary embolism without any evidence of melanoma. The patient surviving 37 months was the only one showing a good response to radiation therapy. This 37 year old woman underwent a resection of the right maxilla and orbit for melanoma in the right eth-

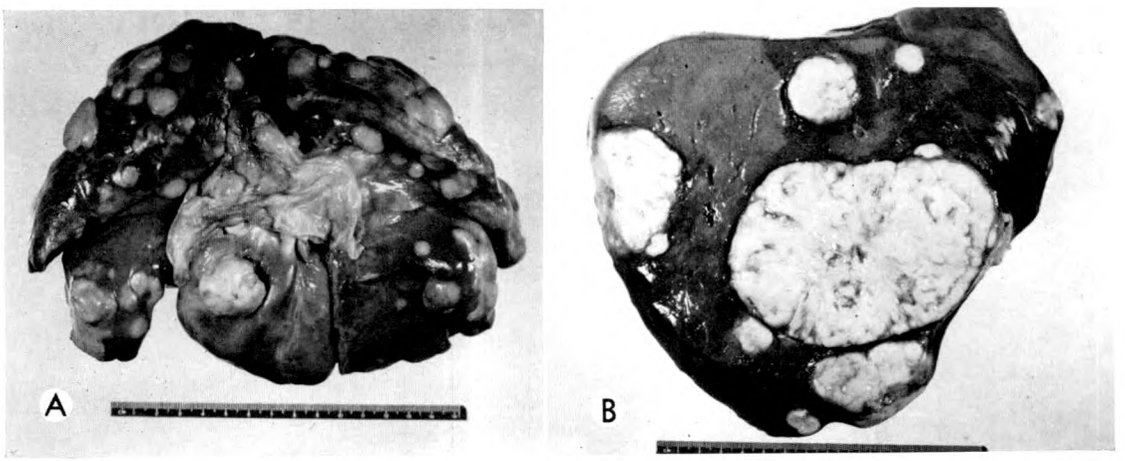


Fig. 7. (*A*) Metastatic melanoma in lung. (*B*) Metastatic melanoma in liver. This 4 year old Negro was our youngest patient. See text.

moid sinus. The tumor recurred locally and metastatic lymph nodes appeared in the right neck. The local recurrence regressed after radiation treatment and the neck lymph nodes diminished in size following implantation of gold radon seeds. However, permanent control was not achieved and the patient died of persistent local and regional melanoma with metastases to the small bowel. A 59 year old man with residual melanoma of the right antrum following heavy radiation therapy given elsewhere was implanted with radon seeds for palliative reasons. This patient died within 5 months.

Two patients with melanoma of the nasal cavity and 1 patient with a melanoma of the lower gum were treated elsewhere with applicators containing radium. In none was regression or improvement noted; all 3 died of melanoma. In a 67 year old man with recurrent melanoma in the right maxillary operative site, low voltage radiation therapy (2,400 r in air delivered through a 3 cm. circular port) controlled bleeding for 3 months. This patient died 12 months later of persistent local melanoma and liver metastases.

Surgery was the treatment of choice for mucosal melanomas at Memorial Center. In 36 of the 43 patients, the primary melanoma was widely excised, including surrounding tissue and structures, as needed, to secure a generous margin. Only 7 patients were not operated on. There were 4 patients with melanomas, one each of the nasal cavity, buccal mucosa, antrum and tonsil, who came for consultation only. Two of these patients (the antrum and tonsil cases) did not return. The remaining 2 cases were seen more than 1 year later; both had disseminated melanoma.

Three other patients were not operated on at Memorial Center. One was the 4 year old Negro boy with buccal mucosa melanoma and cancer of the adrenal gland. He was given radiation treatment and chemotherapy and died 7 months later of melanoma metastases to the lungs and liver (Fig. 7, *A* and *B*). One patient with melanoma of the right maxillary antrum refused operation. He received high voltage radiation therapy; however, tumor regression was poor and he was dead of melanoma in 11 months. The last patient was a 45 year old man with a primary melanoma arising in his right frontal sinus. This tumor was excised at another hospital. Later a right neck dissection was carried out. More recently, a metastatic nodule had been removed from the chest wall. On our first examination, he showed widespread melanoma and was admitted for terminal care. He lived only 2 months.

All 11 patients with no evidence of disease at 5 years underwent wide excisions of their primary melanomas. Six of these cases also had homolateral radical neck dissections. One of these 6 cases, a 61 year old woman with a melanoma of the right upper lip, underwent successful bilateral neck dissection. The surgical specimens from these 7 cases all contained one or more lymph nodes showing metastatic melanoma.

In addition to the 7 successful operations, 12 more neck dissections were performed on 10 patients. Four of these operations were "combined" with resection of the primary melanoma (the so-called "commando" procedure). Two-staged second neck dissections are included in this group. None of these 10 patients survived; 9 were dead of melanoma within 7 to 44 months. One 68 year old man operated on for a melanoma of the extrinsic larynx with metastatic lymph nodes in the right neck died 31 months later of lobar pneumonia. Autopsy revealed no residual cancer.

Of the 9 patients who died, the fatal outcome in 4 was due to distant metastases only. Five patients also developed recurrent melanoma at the site of the neck dissection. In almost one-half of these few patients (44 per cent), the neck surgery was successful in controlling the regional lymph node disease. This limited experience supports our feeling that resectable metastatic cancer in the neck is best treated by a radical neck dissection.

Only a single elective neck dissection was carried out in our entire group of 16 patients undergoing this operation. This 42 year old woman had a residual melanoma in the right nasal cavity which had been unsuccessfully treated elsewhere with both surgery and radiation. The melanoma in the right nasal cavity was excised by a subtotal resection of the right maxilla. Six months later it was elected to perform a homolateral neck dissection although no abnormal neck mass could be felt.

The surgical specimen contained no evidence of metastatic melanoma in the cervical lymph nodes. This patient remained free of disease in the head and neck but died 35 months later of distant metastases to the mesentery and omentum. These findings were confirmed by exploratory celiotomy made elsewhere shortly before the patient died.

No conclusion can be arrived at on the basis of a single elective neck dissection. Fortunately, a surgeon will seldom be confronted with this decision in such a rare variety of mucosal cancer as melanoma. However, it seems reasonable to the author that the total experience gained from this study would furnish strong support for a neck dissection if there is the slightest doubt as to the status of the neck, even in the absence of any clear-cut clinical findings. Melanoma is too virulent a cancer to permit any liberty or chance in its management.

Table III

OVER-ALL END RESULTS

Total no. of patients observed			43
Indeterminate patients			5
Consultation, no treatment	3		
Dead of other causes, NED	2		
Determinate patients			38
Failures		27	
Dead of disease	26		
Living with disease	1		
Successes (NED 5 years)		11	
5 year cure rate percentage			
Absolute (11/43 patients)			25.5%
Determinate (11/38 patients)			28.9%

NED = No evidence of disease.

RESULTS

The results of our treatment in 43 patients are listed in Table III. Both the absolute and net 5 year salvage rates compare favorably with other published reports.[3,4–7] Among the indeterminate cases, 1 patient with melanoma of the larynx died of pneumonia 31 months after surgery and another patient with melanoma of the nasal cavity had a fatal pulmonary embolism 2 months after operation. Both of

these patients were without evidence of melanoma at the time of death.

Among the 11 patients who were well at 5 years, 2 patients died of melanoma during the second 5 years of follow-up. One 61 year old woman with melanoma of the upper lip lived for more than 12 years after surgery and then died of metastases to the small and large bowels. Melanomas seem to have the capability of lying dormant for long intervals and then reappearing as distant metastases.

CONCLUSION

Mucosal melanomas of the head and neck area are rare cancers and the present 12 year experience with 43 consecutive patients is larger than found in most reports. However, when a busy surgical service in a large cancer center sees less than 4 such cases per year, it is unlikely that any single clinic can collect enough cases to be statistically significant. In view of the remoteness of such a possibility, it seemed worthwhile to record in some detail our experience with 43 patients. The nature of the problems and the management thereof may prove of some value to other physicians confronted with these difficult cases.

Probably the most frustrating and ominous trait of any melanoma is the almost total unpredictability of its clinical behavior. To illustrate this erratic quality, 2 cases are briefly presented.

Case No. 44-03-14, a 35 year old man, was admitted after a recent local excision of a small melanoma from the right buccal mucosa. Relevant clinical findings were limited to an indurated 3 cm. scar in the right cheek. As the referring surgeon doubted the adequacy of the operation, a wider excision was made. This surgical specimen contained no residual melanoma; however, although he remained free of tumor in the mouth and neck, he was dead in 12 months of an intracranial melanoma metastasis.

Case No. 11-66-54, a 47 year old man, presented with a small melanoma of the right nasal cavity. This tumor had been partially excised and a metastatic lymph node was removed from the right neck. At Memorial Center, a partial resection of the right maxilla combined with a right neck dissection was performed. Pathologic examination showed residual melanoma in the nose and metastatic lymph nodes in the right neck tissue. Although the prognosis was poor, this man remained well for over 11 years, when he died suddenly of a heart attack.

It is undoubtedly this curious biologic behavior of melanoma which accounts for the salvage of one more case in Stage 2 than in the more numerous Stage 1 cases. In most other forms of cancer (including skin melanomas), the 5 year cure rate for Stage 1 cases is at least double that for Stage 2. At the present time, surgery is the only known treatment of curative possibility for melanoma.

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BASAL CELL NEVUS SYNDROME: ITS ROENTGENOLOGIC SIGNIFICANCE*

REVIEW OF THE LITERATURE AND REPORT OF FOUR CASES

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MULTIPLE, cutaneous basal cell epitheliomas, cysts of the jaws, and an increased number of certain skeletal anomalies constitute the basal cell nevus syndrome. This entity has also been referred to as hereditary cutaneomandibular polyoncosis[24] and nevoid basal cell carcinoma syndrome.[28] It is the purpose of this report to present 4 typical cases of this syndrome with special emphasis on the varied roentgenologic manifestations.

REPORT OF CASES

CASE 1. At the age of 10 years, the patient was noted to have odontogenous cysts and multiple tumors of the skin of the trunk, face and neck. Five years later, he developed keratotic lesions on the palms and soles. Simultaneously, some of the tumors on the face and trunk enlarged and ulcerated. Several were excised and upon microscopic examination were found to be basal cell epitheliomas.

When first seen by us in 1964, he was 22 years of age. He was noted to have light complexion and to be 6 feet, 3 inches tall. The bridge of his nose was broad and depressed, and the distance between the inner canthi was 4 cm., a measurement compatible with hypertelorism. A dental prosthesis was worn because of loss of many teeth. His genitalia and secondary sex characteristics were normal. He had undergone surgical repair of a cleft palate, hare-lip, and bilateral inguinal hernias.

Multiple, smooth-surfaced, translucent nodules, 2 to 5 mm. in diameter, were present on his face, neck and trunk (Fig. 1). Some of these were superficially eroded, others were ulcerated. There were several lesions resembling sebaceous cysts on his extremities and abdominal wall, and numerous milia on his face and trunk. On the skin of the palms and soles, there were keratotic, warty papules admixed with scattered nonkeratotic, erythematous depressions. A pilonidal cyst was present at the base of the spine. There were many scars at sites where cutaneous lesions had been excised previously. The remainder of the physical examination was within normal limits.

There was no family history of any similar lesions of the skin.

The serum calcium was 10.9 mg. per cent and the serum phosphorus 3.7 mg. per cent. The Ellsworth-Howard test for phosphaturic response to parathyroid extract[10] was equivocal, since the patient and control patients failed to



FIG. 1. Case 1. Close-up of the chest showing multiple basal cell epitheliomas and scars from previous excisions.

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Fig. 2. Case 1. Waters' view of the facial bones showing dural calcifications, laminated calcifications in the falx, and widely spaced orbits.

show phosphorus diuresis after receiving the particular parathyroid extract used. The results of other laboratory studies, including complete blood cell count, urinalysis, fasting blood sugar, blood urea nitrogen, total protein and A/G ratio, cholesterol and esters, alkaline phosphatase, protein bound iodine and serum electrolytes, were within normal limits.

Nine lesions removed by electrodesiccation and curettage were submitted for histopathologic examination and were reported to be basal cell epitheliomas including undifferentiated, superficial, solid and adenocystic variants.

Roentgenographic changes were seen in the skull, jaw, shoulders, and chest (Fig. 2, 3 and 4). There was a mottled pattern to the calvarium due either to calcium deposits or osseous metaplasia in the dura. A lamellar type of calcification was present in the falx cerebri. Dentigerous cysts with rudimentary teeth were seen in the maxillae and multiple, tiny cysts were present in the mandible. Several teeth were missing as a result of previous extirpations of odontogenous cysts. There was a lack of normal modeling of the right humerus. The first ribs were flared at the osteocartilagenous junction; the left third rib and the right fifth rib were bifid. The fourth metacarpal was shortened.

Case II. A 43 year old female has been followed at the Skin and Cancer Unit of University Hospital since 1949 for a primary complaint of multiple tumors of the skin. She had noted the beginning of cutaneous lesions during adolescence. When she was 25 years old, some of the lesions underwent ulceration and required excision. Since that time, several hundred tumors of the skin have been removed, principally from the face, neck and upper portions of the trunk. She is a widow and has had

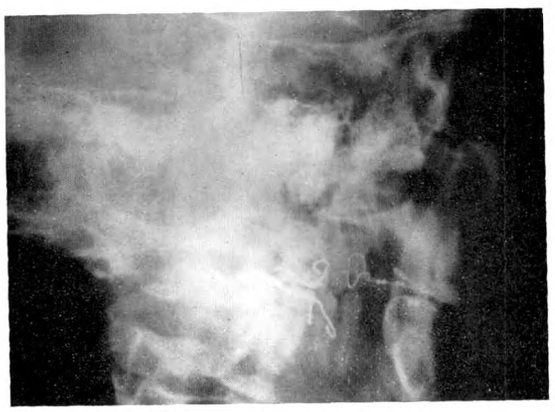


Fig. 3. Case 1. Roentgenogram of the mandible illustrating a recurrent cyst, missing teeth and a dental prosthesis.



Fig. 4. Case 1. Bifid third left rib.

no children, although her menstrual history and secondary sex characteristics are normal. Two sisters and a male first cousin (Case III) have manifestations similar to those of the patient.

Physical examination in 1966 revealed a well-developed, well-nourished, slightly obese, white female. The bridge of the nose was found to be widened and flattened, and the eyes set far apart. A dental prosthesis was in place where several teeth had been removed during treatment of odontogenous cysts. Scattered over the skin of the face, neck, trunk, and extremities were numerous elevated, translucent, pearly, nonulcerated, gray to brown nodules typical of basal cell epitheliomas (Fig. 5). Characteristic keratoses and "pink palmar and plantar pits" of the nevoid basal cell epithelioma syndrome[28] were seen (Fig. 6).

The results of laboratory tests, including determinations of blood calcium, phosphorus, alkaline phosphatase, fasting blood sugar, urea nitrogen, protein bound iodine, and urinalysis, were within normal limits. Ellsworth-Howard tests performed at the National Cancer Institute in 1963 were reported to show hyporesponsiveness to the phosphaturic effect of a potent parathyroid extract.

Roentgenologic examination of the skull revealed moderate hypertelorism and some calcification in the falx cerebri. Roentgenograms of the hands and feet showed shortened fourth metacarpals (Fig. 7) and hallux valgus of both feet. Peri-articular calcification was seen about both shoulders (Fig. 8) and flat roentgenograms of the abdomen showed amorphous calcifications of the type seen with calcified uterine fibromas.

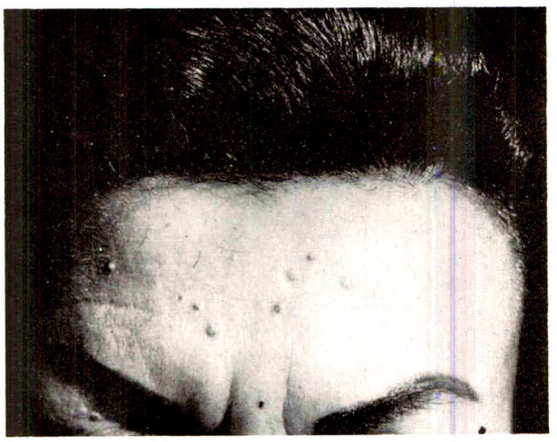


Fig. 5. Case II. Close-up of forehead showing multiple basal cell epitheliomas and milia.



Fig. 6. Case II. Characteristic "dyskeratoses" of the palms.

Numerous skin lesions were removed by surgical excision and electrodesiccation and curettage. All specimens examined histologically were reported to be basal cell epitheliomas.

Case III. A white male, 52 years old, was admitted to University Hospital in 1964 for removal of multiple tumors of the skin of the face and trunk. A number of basal cell epitheliomas had been excised several years before. Other surgical procedures in the past included removal of several dentigerous cysts, repair of a hernia, excision of a pilonidal cyst, hemorrhoid-



Fig. 7. Case II. Roentgenogram of hand showing shortened fourth metacarpal.



Fig. 8. Case II. Calcifications about left shoulder.

ectomy, removal of several sebaceous cysts, and subtotal gastrectomy for peptic ulcer.

Physical examination revealed a well-developed, well-nourished, white man, 6 feet tall, with normal secondary sex characteristics. His eyes were found to be widely spaced and the bridge of his nose broad. There were dyskeratoses on his palms and soles and multiple basal cell epitheliomas on the face, ranging from 3 mm. to 1 cm. in diameter. Many were of the nodulo-ulcerative type. Superficial basal cell epitheliomas were present on the trunk and proximal portions of his extremities. The remainder of the physical examination was normal.

The patient's serum calcium was 9.8 mg. per cent, and phosphorus 3.4 mg. per cent. The Ellsworth-Howard test showed hyporesponsiveness to the phosphaturic effect of an active parathyroid extract.

Significant roentgenologic findings were calcification of the falx cerebri, wide spaced orbits, missing teeth, and spina bifida occulta of C 5, 6, 7 (Fig. 9) and T 1, 2. The rest of the complete skeletal roentgenographic series was normal.

During his stay in the hospital, 30 basal cell epitheliomas were removed by electrodesiccation and curettage.

Case IV. A white female, 49 years old, first noted the onset of a slowly enlarging lesion of the skin of the left temple 20 years ago. In a period of 15 years prior to consultation, many additional tumors appeared on the face, scalp, trunk and extremities. Many of these lesions had been previously removed by electrodesiccation and curettage. When the patient was 25 years old, she had had all her teeth removed for "jaw cysts."

She had but 1 child who died of cardiorespiratory complications at 3 months of age.

Physical examination revealed a short, stout female who appeared to be somewhat mentally retarded. The eyes seemed widely spaced and the root of the nose broad. Characteristic palmar and plantar dyskeratoses and pits were seen. There were many cutaneous tumors (about 200) which had the clinical characteristics of basal cell epitheliomas. These were mainly a few millimeters in diameter, but there was a very large mass covering almost one-half



Fig. 9. Case III. Spina bifida occulta of the cervicodorsal spine.

of the left side of her scalp and extending onto the ear and temple. The small lesions were present on the face, scalp, and sacral regions and a few were scattered on her trunk and extremities.

Routine laboratory findings were within normal limits as were blood calcium, alkaline phosphatase, phosphorus, protein bound iodine, fasting sugar and urea nitrogen. The Ellsworth-Howard test revealed a normal phosphaturic response to parathyroid extract.

The roentgenologic findings were multiple mandibular cysts, incomplete segmentation of cervical vertebrae (Fig. 10), laminated calcification of the falx cerebri, widely spaced orbits, a flattened, bifid, hypoplastic third rib on the right, and bilateral calcifications in what were apparently ovarian fibroids (Fig. 11).

During her hospital stay, the large lesion on the left side of her head was excised and a skin graft applied. Many of the lesions about the face and head were destroyed by electrodesiccation and curettage. Histologic examination of numerous specimens revealed a uniform picture of basal cell epitheliomas.

DISCUSSION

While there are more than 150 recorded cases of this syndrome,[13] it is not possible

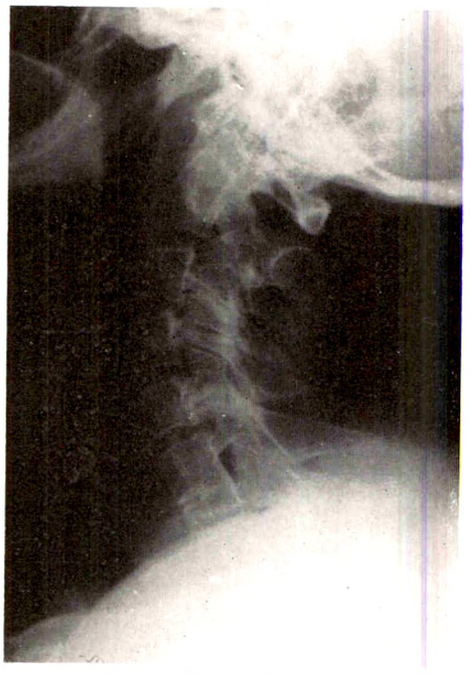


Fig. 10. Case IV. Incomplete segmentation of C6–C7.

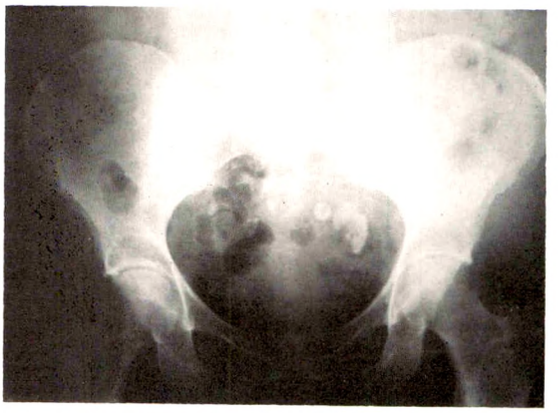


Fig. 11. Case IV. Calcifications in the area of the ovaries.

to enumerate exactly the frequency of the various associated abnormalities because of the incompleteness of the published data. However, the relative frequency of the roentgenologic anomalies has been estimated. A comparison between these estimates and the findings in the 4 cases herein presented are shown in Table I.

Basal cell epitheliomas in this condition usually appear around the age of puberty, but they have been seen in patients as young as 2 years of age.[1,18] The lesions are translucent, slightly raised, skin to brown colored and 1 to 10 or more mm. in diameter. They can, in time, become aggressive, ulcerative and invasive tumors. Microscopically, they are indistinguishable from ordinary basal cell epitheliomas.[22] They develop on exposed as well as nonexposed areas of the skin, most often on the face and trunk. The epitheliomatous lesions of this syndrome differ from common basal cell epitheliomas in their earlier development, multiplicity, and more frequent location on unexposed areas of the skin. They respond to the usual types of therapy used in the treatment of basal cell epitheliomas.[24]

The other essential feature of this syndrome is coexistence of cysts of the jaw which frequently have their onset even before that of the skin lesions. Often appearing in the first decade of life, symptoms from these cysts have been the presenting complaints in about half the reported cases.

TABLE I

ROENTGENOLOGIC CHANGES SEEN IN BASAL CELL NEVUS SYNDROME

	From Literature (13)	Case I	Case II	Case III	Case IV
Multiple cysts of the jaws	++++	*	*	*	*
Mild mandibular prognathism	+	o	o	o	o
Abnormal ribs (bifid; synostosis; partial agenesis; supernumerary)	+++	*	o	o	*
Vertebral abnormalities	+++	o	o	*	*
Shortened 4th metacarpal	++	*	*	o	*
Calcification of dura and/or falx	++	*	*	*	*
Ectopic calcification	+	o	*	o	o
Dystopia canthorum (hypertelorism)	++	*	*	*	*
Frontal and biparietal bossing	+	o	o	o	o
Pelvic calcification	++	o	*	o	*
Cleft palate	−	*	o	o	o

Key: ++++ = very frequent
+++ = frequent
++ = moderately frequent
+ = rare
− = not reported
* = present
o = absent

Those symptoms are swelling of the jaw, dull pain, or drainage of matter from the cysts into the mouth.[13] The cysts are follicular or dentigerous and are lined with epithelium that may be stratified squamous similar to mucous membrane or abnormally keratinized. The cysts range in size from microscopic to several centimeters in diameter and, thus, are grossly visible by roentgenography. Recurrence of cysts after curettage is common, possibly from adjacent microcysts which escaped the curette. Pathologic fractures and, rarely, ameloblastomas[9,13] have been known to develop from such lesions.

Patients with the syndrome frequently develop other skin lesions intermixed with the basal cell epitheliomas. These include milia,[6,7,18] comedones,[8,20] and sebaceous or epithelial cysts. On the palms and soles, a characteristic dyskeratosis in the form of multiple, punctate or linear, erythematous depressions often appears as the patients get older.[1,7,14,28] At times, these lesions begin with warty excrescences simulating arsenial keratoses.

Many of the reported patients have facial resemblance due to frontal and temporoparietal bossing and well developed supra-orbital ridges.[1,12,16,19,27] A broad nasal root, often associated with hypertelorism is also commonly seen.[1,5,12,14,15,18] Extracranial skeletal anomalies are present in about 75 per cent of the cases. More might have been discovered if the total skeleton of each patient had been roentgenographically ex-

amined. Anomalies of ribs, like the bifid, rudimentary, synostotic and cervical ribs, are the most common osseous faults in this syndrome. In "normal" subjects the prevalence of bifid, rudimentary and synostotic ribs per 1,000 has been reported as 6.2, 2.0, and 2.6, respectively in one study[11] and 3.0, 1.2 and 1, respectively, in another.[2] There is a much higher incidence of such abnormal ribs in the basal cell nevus syndrome. Shortened metacarpals, especially the fourth,[4,14] is also a rather frequent finding and suggests some relationship to pseudohypoparathyroidism. Other abnormalities of bones seen less frequently than those mentioned above in the basal cell nevus syndrome are arachnodactyly,[5,14] polydactyly,[9,21] kyphoscoliosis,[5,8,12] spina bifida occulta of the cervicothoracic vertebrae, and failure of complete segmentation of cervical and thoracic vertebral bodies.

Changes in the eyes, described as "dysgenesis oculi neuroblastica gliomatosa," have been noted.[16] These signs were thought to be so characteristic that some have called the condition a fifth type of phakomatosis.[16,17] Blindness secondary to cataract, glaucoma, and coloboma of the choroid has also been reported.[14,23,26]

Other changes seen in the central nervous system are calcifications in the dura, tentorium, choroid, and falx cerebri. These calcifications may have a lamellar pattern.[24] Mental retardation of moderate degree[3,4,12] and congenital hydrocephalus have also been noted.[14,15,26]

Of more serious import is that at least 4 instances of medulloblastoma have been recorded in the syndrome.[13] This is an impressive number which may even be truly higher, because other afflicted children may have died of the brain tumor before enough of the syndrome may have had time to develop to a recognizable degree.

Gonadal abnormalities in this syndrome include ovarian and uterine fibromas frequently with calcification[3,4,14] and in males, hypogonadism and cryptorchidism.[5,9] The shortened metacarpals and gonadal changes in combination raise the question of pos-

TABLE II

COMPARISON OF VARIOUS TYPES OF HYPOPARATHYROIDISM AND THE BASAL CELL NEVUS SYNDROME*

Syndrome	Serum		Tetany	Body Habitus	Parathormone Response	Short 4th Metacarpal	Abnormal Ribs	Ectopic Calcification	Basal Ganglion Calcification
	Ca	P							
Nevoid Basal Cell Epithelioma	N	N	○	Usually normal	Usually hyporesponsive	+	+	+	○
Hypoparathyroidism	↓	↑	+	Normal	Hyperresponsive	○	○	○	+
Pseudohypoparathyroidism	↓	↑	+	Usually short	Hyporesponsive	+	○	+	+
Pseudopseudohypoparathyroidism	N	N	○	Usually short	Usually normal	+	○	+	○
Gonadal Dysgenesis	N	N	○	Usually short	Normal	+	?	○	○

Key: N = normal
○ = absent
+ = present
↓ = decreased
↑ = increased

sible relationship to the syndrome of gonadal dysgenesis.

Some patients who have the basal cell nevus syndrome are hyporesponsive to the phosphaturic effect of active parathyroid extracts.[4,14] This finding, coupled with shortened fourth metacarpals in some patients, suggests a relationship with pseudohypoparathyroidism (Table II).

A study of pedigrees of 25 families exhibiting this syndrome revealed that it is inherited as an autosomal, dominant trait.[1] Penetrance in these families was of high degree and expressivity variable.

SUMMARY

The basal cell nevus syndrome is a hereditary disorder, involving ectodermal and mesodermal structures, which results in a number of clinically and roentgenographically demonstrable abnormalities.

The main features of this syndrome are multiple basal cell epitheliomas of the skin, cysts of the jaws, and various skeletal anomalies.

Hyporesponsiveness to the phosphaturic effect of parathyroid extract, ectopic deposits of calcium, and shortened fourth metacarpals suggest a relationship of the basal cell nevus syndrome to hypoparathyroidism and/or gonadal dysgenesis.

The frequency of medulloblastomas (4 in about 150 reported cases) deserves further investigation.

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Our Case II has been previously reported by Clendenning, Block and Radde (*Arch. Dermat.*, 1964, *90*, 38) as their Case 5.

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PINEAL BODY TUMORS*

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PINEAL tumors are an uncommon form of intracranial neoplasm. The incidence has been estimated to be 0.4 to 1 per cent of all intracranial neoplasms by Zülch.[18] Kernohan and Sayre[7] reported only 35 pinealomas in over 4,000 tumors of the central nervous system. In the last 20 years there have been 16 patients with primary pineal body tumors at the Walter Reed General Hospital, Washington, D. C. The present report will deal with the treatment of such tumors and especially the role of radiation therapy in their management.

CLINICAL DIAGNOSIS

The normal function of the pineal body is not as yet clearly understood. The symptoms and physical findings of tumors of the pineal body are primarily related to those expanding lesions in this region which can obstruct the aqueduct of Sylvius, leading to increased intracranial pressure and internal hydrocephalus. Characteristic findings result from involvement of certain regional anatomical structures. In specific localization to the occulomotor apparatus, there is loss of upward conjugate deviation of the eyes (Parinaud's syndrome) and abnormalities of pupillary reflexes. Posterior tumor growth is indicated by loss of downward conjugate deviation of the eyes, impairment of hearing, and cerebellar signs such as staggering gait, a positive Romberg sign, nystagmus, and varying degrees of ataxia. Inferior and anterior extension into the hypothalamus and midbrain can be inferred by hypersomnia, and diabetes insipidus. Pyramidal and thalamic symptoms occur when the neoplasm extends laterally. Certain patients with pineal tumors have been found to have delayed gonadal function and others have shown precocious puberty.

Roentgenograms of the skull may show unusual calcification or shift of a calcified pineal gland. Air studies will usually reveal dilated lateral ventricles, often with dilatation of the anterior portion of the third ventricle. The posterior portion of the third ventricle will usually show a midline filling defect without lateral shift. Arterial angiograms may be consistent with internal hydrocephalus, whereas the venogram phase may show the vein of Galen to be displaced superiorly, losing its normal curve as it circumvents the splenium of the corpus callosum.

PATHOLOGY

In the 7 patients that were autopsied at Walter Reed, the lesions presented the characteristic range of gross features. Because of the location of the pineal body, the tumors usually invade the third ventricle from the rear and often fill it; they spread into the tectum of the midbrain with compression and downward deviation of the aqueduct and tegmentum; and they may raise the splenium of the corpus callosum. The tumor is soft, fleshy, often hemorrhagic and necrotic. Such a picture is shown in Figure 1 and is almost diagnostic.

The posterior lobe of the pituitary may be involved discontinuously or continuously via the pillars of the fornix or floor of the third ventricle (Cases 3, 4, 5 and 8). It may even occur there as a sole lesion. Rubin and Kramer[11] have reported 8 cases of ectopic pinealoma where the pineal body was normal and the tumor in the hypothalamic region in each case was a primary and not a metastatic tumor. Al-

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From the Radiology Service and the Pathology Service, Walter Reed General Hospital.
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though none of our cases occurred only in the pituitary, 1 case (Case 8) did have residual tumor only in the pituitary region. It was a true teratoma and all areas of tumor elsewhere had disappeared subsequent to irradiation. The pineal body could not be found.

In Case 6 growth occurred only into the midbrain. An attempt to get a tissue diagnosis via the third ventricle failed as no tumor was present there. No treatment was given other than a shunt (Fig. 2). Case 5 presented a similar picture although there was some growth into the third ventricle. Since no exploration was attempted in this case, diagnosis was not established prior to autopsy.

Dorothy Russell[12] has classified pineal tumors according to the following plan:

I. Teratomas:
  (1) typical and teratoid
  (2) atypical
II. Pinealomas:
  (1) pineoblastomas
  (2) pineocytoma
III. Glial and other forms
IV. Cysts

Of the 12 cases examined histologically, 8 were composed of the 2 cell pattern (resembling a seminoma) of what is generally classified as an atypical teratoma after Russell and Rubinstein.[13] This has often been simply designated as pinealoma in the earlier pathology literature. This 2 cell pattern is characterized by a large cell with abundant cytoplasm and generally clear cut cytoplasmic border. Intermixed are many small, dark "lymphocytes." They have scant cytoplasm and generally are clustered. The pattern is shown in Figure 3.

One case mentioned above (Case 8) had a proven 2 cell atypical teratoma pattern initially by biopsy of the pineal tumor. Following irradiation, there was improvement, but he died subsequently of a neoplasm in the pituitary area. This was a true tera-

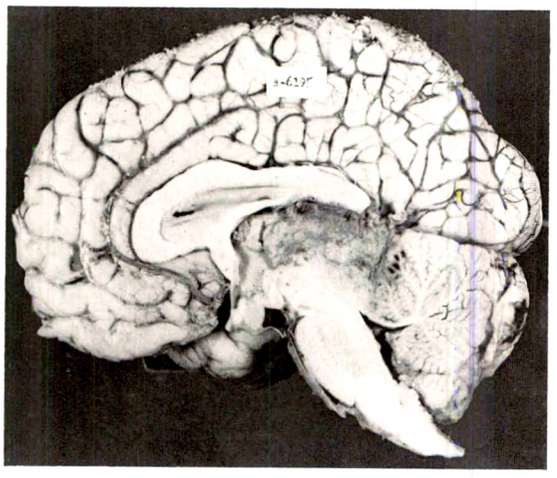


Fig. 1. Case 3. Pineal body tumor in a sagittal brain section. The location, downward depression of the aqueduct, and growth into the third ventricle are diagnostic.

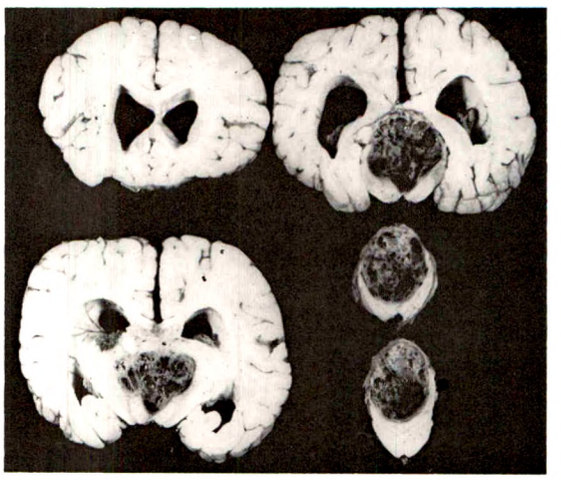


Fig. 2. Case 6. Pineal body tumor in coronal sections with extension into the midbrain.

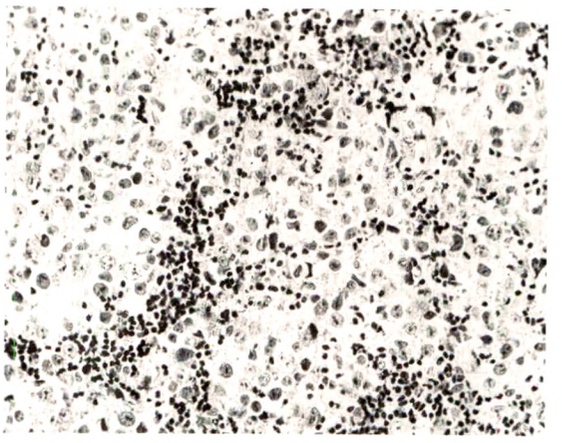


Fig. 3. The 2 cell tumor pattern (seminoma, atypical teratoma) (240 ×).

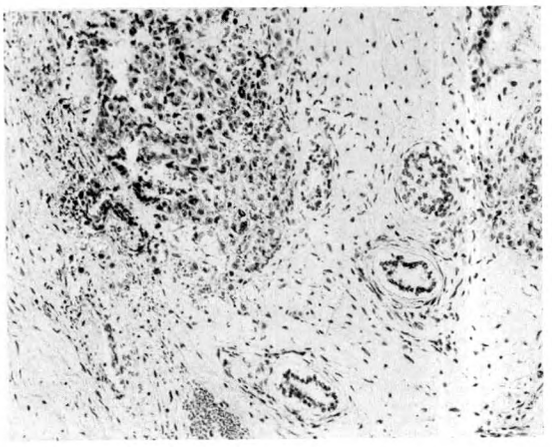


Fig. 4. Case 8. Teratoma in the pituitary. The 1 focus of 2 cell tumor found is included in the photograph (110 ×).

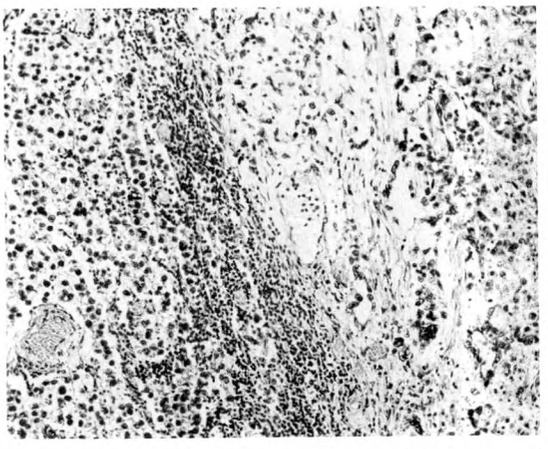


Fig. 5. Case 5. The margin of the 2 cell tumor and the embryonal carcinoma (110 ×).

toma (Fig. 4) with only 1 small focus of the 2 cell pattern found. We believe that these are 2 separate tumors, and that they occurred coincidentally, or perhaps that they are related as are testis seminomas and teratomas. We do not feel that all atypical teratomas have true teratoid elements present as suggested by Russell *et al.*[12,13,14] In this connection, Case 10 had a central core of tumor histologically identical to a testicular embryonal carcinoma. Encircling this, but separated by an abrupt transition, is the 2 cell pattern. It is the 2 cell pattern that is infiltrating adjacent brain stem. There is no mixture of cell types (Fig. 5).

There are 2 cases of pineocytoma (Cases 1 and 11) and 1 of pineoblastoma (Case 2). In the former cases, the tumor mimics the normal pineal elements. In the latter, the cells are small, round, dark and have little cytoplasm as in a medulloblastoma or a neuroblastoma (Fig. 6 and 7).

METHOD OF TREATMENT

In former years, attempts at total surgical extirpation of pineal body tumors have been made. However, because of disappointing results and high morbidity, such operations have been abandoned in favor of more conservative measures. Hor-

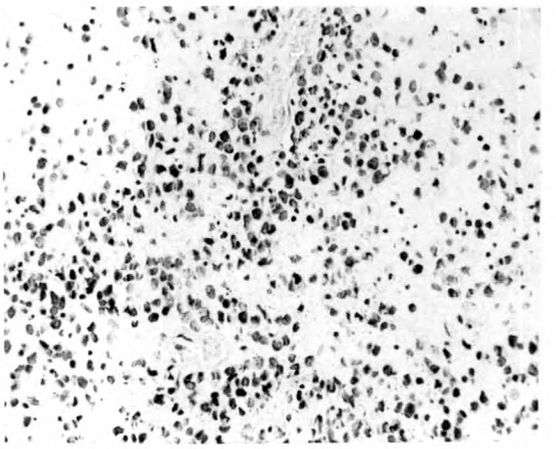


Fig. 6. Case 1. Pineocytoma. The cells, the stroma, and the loose arrangement mimic the normal pineal body (240 ×).

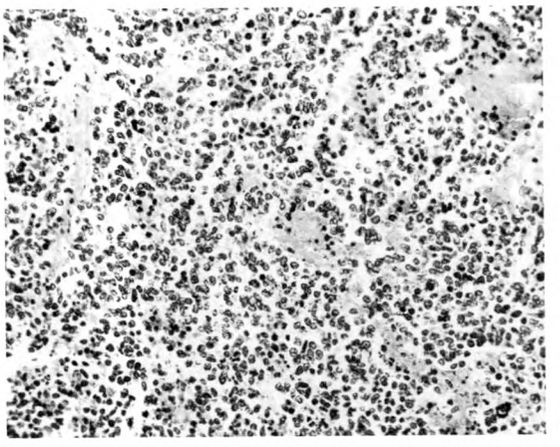


Fig. 7. Case 2. Pineoblastoma. Note the similarity to a medulloblastoma or neuroblastoma (240 ×).

rax[4] reported a series of pineal tumors in which 10 patients had gross operative removal. At the time of his report, only 3 of these 10 were alive and these 3 had received postoperative irradiation. The more generally accepted method of treatment today is to relieve the increased intracranial pressure either by ventriculocisternostomy (Torkildsen),[16] subtemporal decompression (Horrax)[5] or third ventriculostomy (Stookey and Scarff).[15] This surgical treatment is then followed by radiation therapy.

In the present series, 14 patients had some form of decompressive surgery as indicated in Table 1. Two of these patients died shortly after operation, 1 died at 4 months without having irradiation, and 10 subsequently underwent irradiation. The time between surgery and the initiation of radiation therapy varied from 1 to 2 weeks. Supervoltage x-ray at 1 mv., 2 mv., or Co^{60} was employed with a half value layer respectively of 3.6 mm., 7.1 mm., and 11 mm. of Pb. Field size varied depending on estimates of tumor volume. Either lateral opposing portals or rotational technique was employed. The dose as shown in Table 1 varied from 4,000–5,600 r in 5 to 6 weeks. Replacement hormonal therapy was given as needed and included steroids, pitressin, and thyroid. Electrolyte replacement was closely regulated in those cases having diabetes insipidus.

RESULTS

The histologic type, method of treatment, and follow-up data for each of the 16 cases can be seen in Table 1. The follow-up

TABLE 1

PINEAL BODY TUMOR SERIES

Case	Age	Sex	Pathology		Surgical Procedure	Radiation	Follow-up
			Surgical Biopsy	Autopsy			
1	12 yr.	M	None	Pineocytoma	T	None	Postoperative death
2	3 yr.	F	None	Pineoblastoma	E & D	None	Died 2 yr.; (undiagnosed PTA)
3	19 yr.	M	Atypical teratoma	Atypical teratoma	T	None	Postoperative death
4	23 yr.	M	None	Atypical teratoma	None	None	Died 6 mo.; (undiagnosed PTA)
5	25 yr.	M	None	Atypical teratoma Embryonal carcinoma	None	None	Died 6 mo.; (undiagnosed PTA)
6	32 yr.	M	None	Atypical teratoma	T, E & D	None	4 mo.
7	23 yr.	M	None	None	T	5,600 r	Died 2 yr.
8	19 yr.	M	Atypical teratoma	Teratoma in pituitary only	E & D	4,000 r	Died 3 yr.
9	22 yr.	M	None	None	T	4,257 r	Died 3 yr.; cause unknown
10	35 yr.	M	Atypical teratoma	None	E & D	4,009 r	Died 11 yr.; bronchopneumonia
11	21 yr.	M	Pineocytoma	None	E & D	4,582 r	Died 11 yr.; cause unknown
12	24 yr.	F	Atypical teratoma		E & D	4,000 r	L & W 16 mo.
13	14 yr.	M	Atypical teratoma		T	4,238 r	L & W 7 yr.
14	25 yr.	M	None		T	4,032 r	L & W 12 yr.
14	25 yr.	M	None		T	4,065 r	L & W 8 yr.
16	16 yr.	M	Atypical teratoma		T	5,000 r	L & W 18 mo.

T = Torkildsen.
E & D = Exploration and Decompression.
PTA = Prior to Autopsy.
L & W = Living and well.

is current and complete on all cases. There were 3 cases that had clinical diagnoses other than pineal tumors until necropsy. Two cases died shortly after surgical attempt at decompression and 1 case died at 4 months after a Torkildsen operation only. Thus, there were 10 cases having definitive treatment by surgical decompression and postoperative irradiation. Of these, 5 are alive and free of tumor at 12½ years, 8½ years, 7½ years, 16 months, and 18 months. Five are dead having lived 11½ years, 11 years, 3 years, 3 years, and 2½ years following diagnosis and treatment. In the 3 cases undiagnosed until autopsy, the average time between symptoms and death was 6 months.

There were 12 cases with a proven histologic diagnosis. Of those 4 cases having a diagnosis made only by clinical and roentgenographic means, 2 are living and 2 are dead.

DISCUSSION

From the present study and the experience of others,[2,4,5,6] there can be little doubt that surgical decompression (ventriculocisternostomy) followed by radiation therapy can produce significant palliation as well as cure in some cases. The poor results of attempt at complete surgical extirpation alone have been referred to above. It would appear that surgical decompression permits effective radiation therapy with subsequent tumor regression. Although Torkildsen[17] reported 1 case of significant long-term palliation by ventriculocisternostomy alone, there is no significant series in the literature where this procedure alone was done. Likewise, there is no significant series of pineal body tumors treated by irradiation without some form of antecedent surgical decompression. It is difficult to conceive that ventriculocisternostomy in itself could initiate tumor regression.

As early as 1925, Horrax and Bailey[6] reported pineal body tumors with metastases. It is well-recognized that spread can occur by direct continuity, by seeding through the cerebrospinal fluid pathways and through the blood stream. In 1956, Fowler, Alexander, and Davis[2] reported 2 cases with metastases to the cerebellum and 1 with metastases to the lumbar spine. They reviewed the literature and found 37 such cases among 22 separate reports. They concluded that the treatment of choice for tumors of the pineal body is surgical decompression to relieve increased intracranial pressure preferably by a ventriculocisternostomy followed by irradiation of the entire cerebrospinal axis. The true incidence of metastases to the spinal column with pineal body tumors is difficult to ascertain because of the small number of cases in the various series reported in the literature. Horrax[4,5] reported 3 cases of metastases in a total of 22 cases, but none of these involved the spinal column. In a recent unpublished review of 100 cases of pineal body tumors at the Armed Forces Institute of Pathology the incidence of spinal column metastases has been found to be 8 per cent.

In the present series there are no cases of spinal column metastases. The cause of death has been local recurrence or local extension of the tumor with wide invasion of contiguous anatomical structures. Fowler *et al.*[2] pointed out the morphological similarity between the small cells of the pineal tumor and mononuclear cells of hematogenous origin. They stressed that with a routine examination of the spinal fluid the significance of a pleocytosis might pass unrecognized. Russell and Rubenstein[18] consider these small mononuclear cells as precursors of the large parenchymal tumor cells. It is conceivable that tumor implants from these small mononuclear cells in the cerebrospinal fluid can take place. The exact number of such cells needed and the tumor-host conditions necessary for implantation are open to speculation.

In 1954, Kitay *et al.*[8,9] reviewed the literature on pineal tumors associated with endocrinopathies and noted a correlation between histology and the particular endocrine symptom. True parenchymatous

pineal tumors had a high degree of association with depressed gonad function while nonparenchymatous lesions like gliomas or teratomas that destroyed the pineal frequently were found in patients with precocious puberty. Such data suggest that the pineal probably produces an inhibitory gonadal hormone. In 1959, Lerner, Case, and Heinzelman[10] isolated a chemical substance which they named melatonin (5-methoxy N-acetyltryptamine) from the pineal body. In the same year, Giarman and Day[3] showed that the pineal body also contains large amounts of serotonin as well as other biogenic amines. In 1964, Cohen, Wurtmann, Axelrod, and Snyder[1] reported that the pineal body of the rat contains very large amounts of serotonin, a melatonin precursor and the enzyme required to make it. They suggested that the pineal body acts as a form of a transducer of environmental stimuli. Light, in particular, is believed to effect the synthesis of certain compounds in the pineal body which are hormones which subsequently enter the blood stream and alter the endocrine system. Chemical studies by Cohen *et al.*[1] were done in tumor tissue in the case of a 14 year old boy with delayed puberty and a metastatic parenchymal pinealoma. The presence of the melatonin forming enzyme hydroxyindole-O-methyl transferase (HIOMT) was found as well as melatonin and very high levels of serotonin. The exact significance of these findings awaits further clarification, but raises the possibility of future diagnostic urine assay techniques for pineal methoxy-indoles and their metabolic products in tumors of the pineal body.

CONCLUSION

Pineal body tumors have been shown to be sensitive to irradiation following relief of intracranial pressure by surgical decompression. The atypical teratoma described by Russell and Rubenstein[13] and referred to simply as pinealoma by others appears to be the most sensitive histological type to irradiation. There is a close resemblance in histological appearance and response to irradiation between this tumor and the seminoma of the testis as well as the dysgerminoma of the ovary. Although lower radiation doses cause tumor regression, doses in the order of 4,000 to 5,000 r in 5 to 6 weeks appear necessary for tumor sterilization. The radiation response of these tumors lends support to the concept that the atypical teratoma (seminoma or 2 cell tumor) is a distinct tumor which usually does not have true teratomatous elements in it. The incidence of spinal column metastases is low. In view of the possible sequelae of wide field irradiation of the central nervous system, irradiation of the entire cerebrospinal axis does not appear warranted. Correct estimation of true intracranial tumor volume is imperative. Decompression for increased intracranial pressure by ventriculocisternostomy has proven most helpful and is recommended rather than attempt at wide surgical excision of the primary neoplasm.

SUMMARY

Sixteen patients with pineal body tumors have been evaluated. Ten patients were treated definitively with a combination of surgical decompression for increased intracranial pressure followed by postoperative irradiation. Five of these patients lived beyond 5 years and 2 are living and clinically free of tumor at 16 and 18 months postirradiation. Three patients had significant palliation, but died between 2 and 4 years post treatment. Three patients were not diagnosed as having pineal body tumors until autopsy. Two patients died postoperatively following attempt at decompression for increased intracranial pressure and 1 patient died 4 months after a Torkildsen procedure without having postoperative irradiation. An early clinical diagnosis followed by decompressive surgery and postoperative irradiation can be expected to improve results in such tumors.

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INTERNAL STRABISMUS SECONDARY TO INTRACRANIAL EXTENSION OF CANCER OF THE NASOPHARYNX CURED WITH RADIATION THERAPY*

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OUR interest in the treatment of carcinoma of the pharynx with fractionated doses of roentgen rays was first aroused by a paper by Coutard and Baclesse of Paris, France, published in this JOURNAL in 1932. Since we had already adopted the low intensity radium needle technique advocated be Stanford Cade[3] in London in 1929 for accessible lesions of the pharynx,[11] we reserved the French roentgen ray method for the inaccessible lesions in the nasopharynx. A recent study of our material indicated that good results could be expected in the early primary tumors in the nasopharynx called transitional cell epitheliomas by some pathologists and epitheliomas Stage IV by others. In our files, we located 57 records labeled cancer of the nasopharynx. When 6 cases of low grade squamous cell carcinoma of the nasal passage and pharynx, 1 adenocarcinoma limited to the nasal passage and 1 rhabdomyosarcoma of the upper pharynx were excluded, 49 patients with true transitional cell epithelioma receiving treatment were left. A survey indicated that 10 patients (20.9 per cent) of the 49 who had a chance to be cured with fractionated roentgen ray therapy were alive for 8 to 29 years. In this group, one was alive 8 years, one 9½ years, one 10 years, three 12 years, two 20 years, one 25 years and one 29 years. Three patients, probably well, were lost to follow-up at 8, 10, and 12 years. If they could be proved to be well our cure rate would rise to 26.5 per cent (Table 1).

Most of our failures occurred in cases with distant metastases or invasion of the intracranial cavity. A study[12] of these complications was published in 1939.

The authorities with much experience agree that intracranial extension of nasopharyngeal cancer carries with it a very poor prognosis. In Portmann's textbook[15] on Therapeutic Radiology, del Regato states: "The presence of cranial nerve paralyses is an unfavorable prognostic sign." In Pack and Ariel's textbook[14] dealing with cancer of the head and neck, Simmons and Ariel state that none of their patients with intracranial invasion from cancer of the nasopharynx was alive at 5 years.

Walter T. Murphy's textbook,[13] titled "Radiation Therapy," contains the following statement: "Evidence of nerve compression invites almost a hopeless prognosis in differentiated squamous cell cancer. The signs are not so foreboding in the pa-

TABLE I

Cancers of Nasopharynx	57
Transitional Cell Cancers	49

No. of Well Patients	Patients Well When Lost
1 8 yr.	
1 9½ yr.—Strabismus	
1 10 yr.	1
3 12 yr.	1
2 20 yr.	1
1 25 yr.—Strabismus	
1 29 yr.—Strabismus	
—	—
10	3

Well 8 to 29 years—13 of 49 = 26.5%.

* Presented at the Sixty-seventh Annual Meeting of the American Roentgen Ray Society, San Francisco, California, September 27–30, 1966.

tient with anaplastic squamous cell cancer."

Reprints[4,5] just received from Peter Clifford, working in the Kenyatta National Hospital in Nairobi, indicate that, contrary to previous beliefs, cancer of the nasopharynx is relatively common in East Africa where no radiotherapy is available. Photographs of striking temporary improvement produced in advanced cases with nitrogen mustard given with anticoagulants are included but no real cures are reported.

In checking over our scanty material we were pleasantly surprised to find that 3 of 6 treated patients with internal strabismus, caused by an extension of nasopharyngeal cancer through the foramen lacerum producing pressure on the 6th cranial nerve, were well and symptom-free for periods of $9\frac{1}{2}$, 25, and 29 years after radiotherapy.

At first glance, this small number of good results seemed to be of little significance but when a rapid survey of the American literature and some of the reports published in other countries revealed only 4 similar results, a more detailed study seemed indicated.

Actually, Scanlon *et al.* of the Mayo Clinic recently reported 2 of 12 cases with 6th nerve paralysis alive at 5 years, but in a personal communication[16] Scanlon stated that 1 now has metastases in the thoracolumbar spine and one rib so that this case cannot be designated as a cure.

In 1954, Pinto Vieira[17] of Brazil reported 5 year survivals in 5 of 31 patients with cancer of all types originating in the nasopharynx, and treated exclusively with radiotherapy. In a recent communication, he states that he now has 12 of 48 patients alive and well for 5 or more years (25 per cent). Two with internal strabismus are now well 7 and 10 years after therapy.

In 1942, Lenz[10] reported 44 cases with malignant tumors of the nasopharynx, 13 (27.6 per cent) of which were alive and symptom-free 5 years after orthovoltage roentgen ray therapy was given. Since Purdy Stout was the chief pathologist at the Presbyterian Hospital in New York where Lenz worked in 1942, his tumors were divided into the following categories: cylindroma 3, well differentiated epithelioma 2, slightly differentiated epithelioma 5, undifferentiated epitheliomas 7, lymphoepitheliomas 17, and lymphosarcoma 10. In a recent letter, Lenz informed us that he has one 30 year survivor who had involvement of the 5th and 6th intracranial nerves, destruction of the tip of the petrous portion of the temporal bone, and a tissue diagnosis of lymphoepithelioma. Since Ewing stated in 1929 that "it is often difficult to differentiate microscopically between lymphosarcoma, lymphoepithelioma and transitional cell carcinoma," it seems reasonable to include this patient in our group of long time cures of transitional cell carcinomas of the nasopharynx with intracranial extension.

W. D. Rider, working in the Princess Margaret Hospital in Toronto, has just informed me that he has located a patient treated for 5th and 6th nerve imvolvement secondary to a transitional cell carcinoma of the nasopharynx, well and symptom-free for $10\frac{1}{2}$ years after treatment of the base of the skull with radiation. The primary lesion was treated successfully 11 months before the intracranial lesion was discovered.

It has been known for many years that cancer of the nasopharynx has a high incidence in China and Paul Hodges was good enough to ask Chun Yü, who once worked with him in Chicago and is now Chief of the Radiological Department in the Veterans Hospital in Taiwan, to write to us relative to his experience. Dr. Yü states that during 2 years spent in his present position he has seen 210 nasopharyngeal cancers and is quite sure that many others have not consulted him. In fact, he believes this to be the commonest type of cancer in Southern China. He has treated patients with internal strabismus with radiotherapy but cannot report any significant results after only 2 years of experience.

Letters have also been exchanged with Stephen D. Sturton at the Hong Kong Sanitarium and Hospital. His radiotherapy department was opened in 1954 but it has been impossible for him to compile accurate statistics because some patients who did well never returned, while those with relapses went to their general physicians or herbalists. In 1965, Wen, Sturton and Sturton[18] published a study of 450 cases seen in Hong Kong from 1954 to 1964, but no mention was made of therapeutic results.

So this leaves us with reports of 7 cases including our own with internal strabismus secondary to intracranial invasion of cancer of the nasopharynx, free of symptoms for 7 or more years after radiotherapy which can be considered as possible cures. Certainly, our 2 patients, well for 25 and 29 years, and Lenz's patient, well 30 years, can be called actual cures and a recent examination of our third patient, alive and well for 9½ years with no evidence of cancer indicates that he may also be cured. Rider's patient, well 10½ years, and Vieira's case, well 10 years, also fall in this category. Only when a long-time study of a large number of patients has been made can we determine the survival time indicating a real cure.

TECHNIQUE

Many radiotherapists are now changing from orthovoltage to the cobalt 60 teletherapy and supervoltage roentgen-ray therapy for treatment of tumors of the nasopharynx. It is true that larger depth doses can be delivered with lesser skin changes with the newer equipment, but those of us who have encountered irreparable ill effects produced in the deep seated normal tissues tend to favor the smallest effective quantity of deep radiation. Fortunately, the radiosensitive transitional cell carcinoma is the one most frequently encountered, but the estimation of the correct dose for the destruction of a tumor that often extends from the region of the fossa of Rosenmüller through the posterior wall of the pharynx and beneath the floor of the skull to invade the bone or pass upwards through natural openings into the cranial vault poses a difficult problem.

Any attempt to calculate tumor doses in these areas containing bone and soft tissue is somewhat beyond the author's capabilities. Therefore, all of the data that can be ascertained accurately will be set down in the following histories of our successful cases so that the techniques can be duplicated by any radiotherapist who is familiar with orthovoltage roentgen ray machines and the measurement of doses in air.

SUCCESSFUL CASES

CASE 1. (Fig. 1). This 47 year old man (L.V.H.) was referred to our clinic on March 6, 1957 with a long history of "chronic allergic sinusitis." The left ear had been "stopped up" at intervals for a period of about 2 years. A loss of taste, deafness in the left ear with tinnitus and numbness in the left cheek had been present for about 4 months. During the same period, he had lost 22 pounds of weight and developed an intermittent diplopia and hoarseness.

At admission, he had a left sided internal strabismus with double vision, a lagging of the left vocal cord, numbness of the left cheek and deviation of the tongue to the left.

Vertical roentgenograms of the skull revealed an area of destruction in the floor of the left middle fossa, including the foramen lacerum and the foramen ovale and measuring about 2.5 cm. in diameter. A submucosal induration in the left side of the upper nasopharynx could be felt, but biopsy studies of tissue removed from this region by an otolaryngologist revealed no evidence of cancer. Experienced specialists have reported such tumors growing from inside the eustachian tubes from which no diagnostic tissue could be removed. The neurologic and roentgenologic findings were considered ample evidence on which to base a diagnosis and roentgen ray therapy was started.

Opposing beams of 220 kv. roentgen rays were directed through 10×10 cm. portals[12] placed in each temple, extending from the lateral border of the orbit to the posterior edge of the mastoid process so as to include the upper nasopharynx and the points of emergence of the cranial nerves into the cranial vault. A

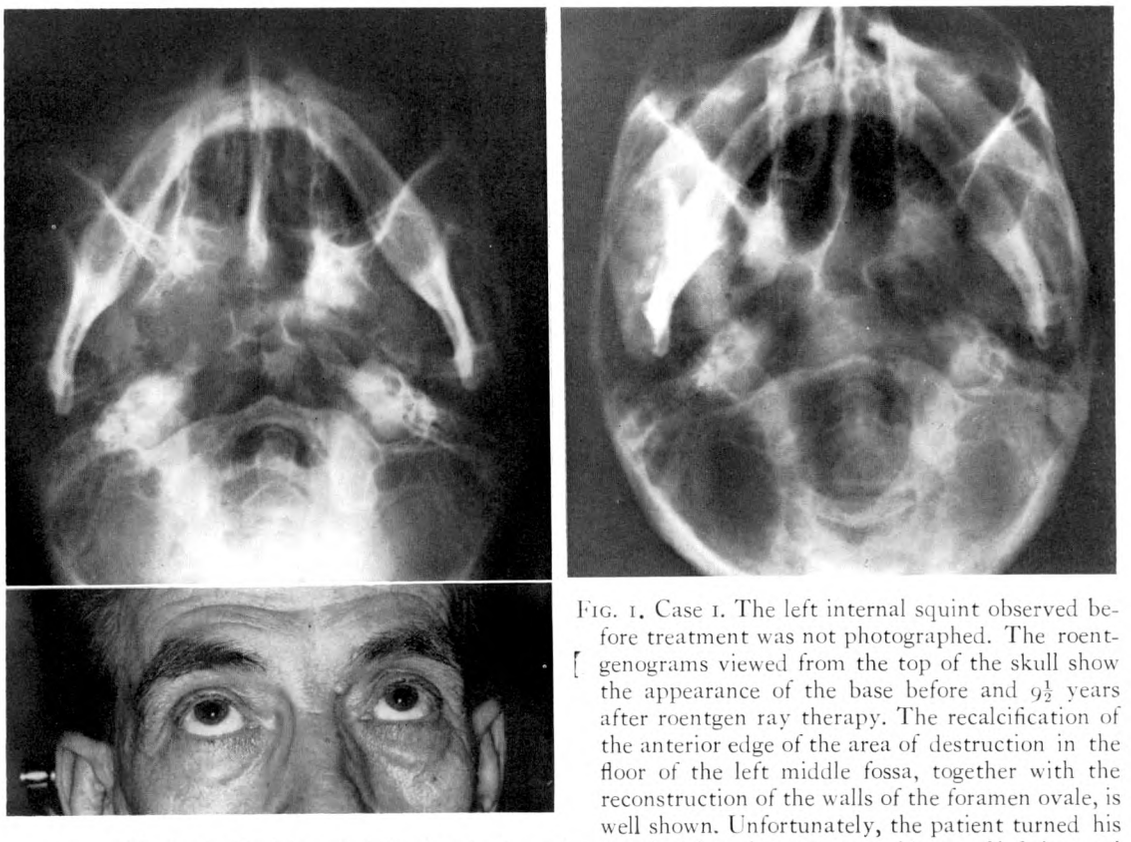


Fig. 1. Case 1. The left internal squint observed before treatment was not photographed. The roentgenograms viewed from the top of the skull show the appearance of the base before and 9½ years after roentgen ray therapy. The recalcification of the anterior edge of the area of destruction in the floor of the left middle fossa, together with the reconstruction of the walls of the foramen ovale, is well shown. Unfortunately, the patient turned his eyes upward instead of looking straight ahead when photographed but there was no evidence of left internal squint at 9½ years.

Thoraeus filter, made up of 0.5 mm. of tin, 0.25 mm. of copper and 1.0 mm. of aluminum, was used with a target skin distance of 50 cm. Doses of 300 r measured in air were given daily except Sunday to alternate sides until a total of 3,000 r (air) was given to each portal in a period of 22 days.

The early treatments produced swelling of both parotid glands as well as nausea. These symptoms were controlled with 25 mg. thorazine tablets. One was taken before each treatment and repeated at 3 or 4 hours, if necessary. (When such patients develop vomiting, the medication should be given in the form of suppositories. Needless to say, they should stay at rest until relieved.) After 5 or 6 treatments, these symptoms gradually disappeared. Before thorazine became available, nembutal tablets and suppositories were used.

At the end of the roentgen ray series, the strabismus and double vision had disappeared. He developed the usual sore throat with difficulty in swallowing during the series, but no nasal tube was used and he began to slowly improve after 8 days. A tan with complete epilation appeared slowly in both temples.

At 3 months he felt much better and had no double vision or numbness in the left cheek. He still had intermittent hoarseness and occasional blockage of the left eustachian tube and was referred back to his otolaryngologist because of discharge from the left auditory canal.

Recently, after 9½ years, the patient was asked to come in for roentgenologic studies and a photograph. He had been wearing a hearing aid for some 4 years because of increasing deafness in the left ear and still had some deviation of the tongue to the left but no evidence of damage of the left 5th or 6th cranial nerves or induration in the pharyngeal wall could be detected. He had the dryness of his mouth, found in all patients treated over the parotid gland, but stated that he felt unusually well. He had a peculiar speech defect with he claimed was present at his first visit, but it was not noted in our first examination record. A vertical roent-

genogram of the skull showed smooth recalcification of the anterior edges of the defect in the floor of the left middle fossa with restoration of the foramen ovale and the tip of the petrous portion of the temporal bone.

Comment. For those who feel that some estimation of tissue dosage must be attempted even though it be only an approximation, let us say that the mid-point of the anterior fossa lies about 7.0 cm. below the skin surface of each temple in a person of average size. Using 200 kv. and a filter of 2.0 mm. of copper and a layer of 1/8 inch of bakelite over the end of the cone and not changing the other factors, the tissue dose at the point described should amount to about 3,480 r. The use of 220 kv. and the increase in filtration should increase this figure to approximately 3,500 r, the dose originally recommended by Coutard. Of course, the effect of the complex bony structures in the base of the skull is ignored. Using the conversion factor of 95 to 96 per cent recommended by Murphy, the mid-line dose becomes approximately 3,360 rads. The factors which are known to be only almost accurate in these conclusions render the final result to be much less dependable than one calculated by an engineer for power generated by a man-made engine, which can be accurate to the third decimal place or better. We are inclined to agree with Lampe[9] who, after studying a series of case histories indicating that tissue doses of 3,650 r to 4,700 r can be safely given to the brain stem and spinal cord with orthovoltage equipment in 21 days, states that "probably a definite radiation tolerance dose will never be known—."

CASE II. (Fig. 2). This 25 year old woman (Mrs. L.M.C.) was admitted to the hospital on February 24, 1941 complaining of severe headaches and nausea for 6 months and right sided deafness, double vision and right internal strabismus for 3 months. Before admission, a radical operation was performed on the right antrum without relief of symptoms. Soon after-

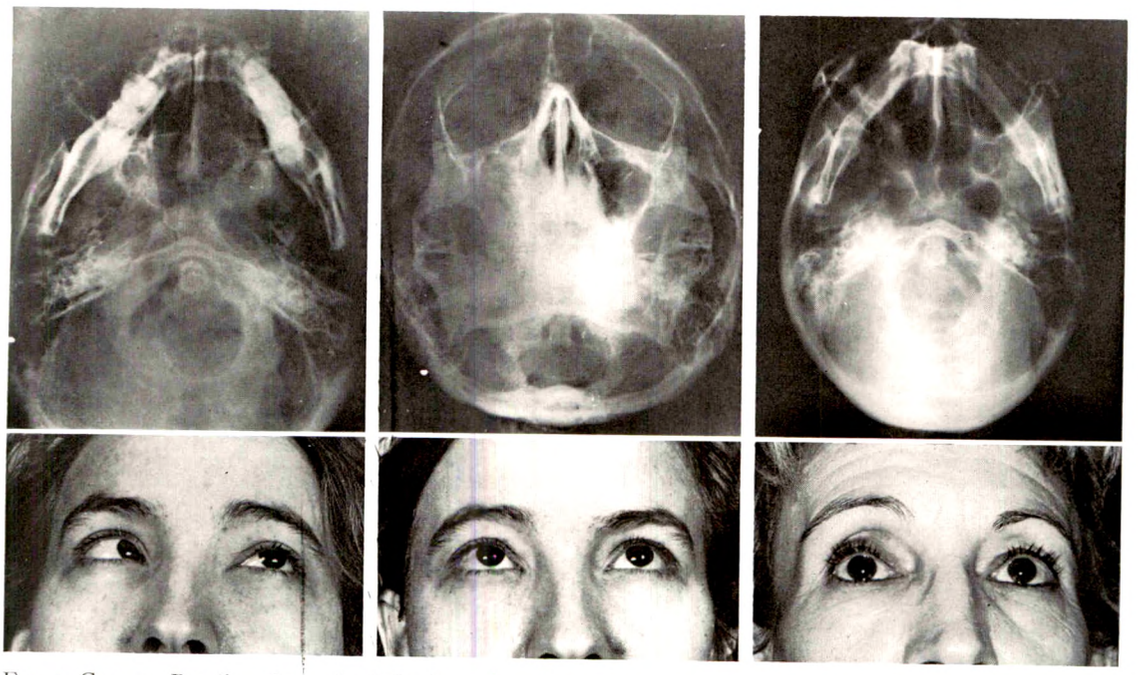


FIG. 2. Case II. Reading from the left the pairs of roentgenograms and photographs were made before treatment on February 24, 1941, and at 6 months and 25 years later. All photographs were made while the patient looked straight ahead and the rapid and lasting recovery is evident. The absence of destruction in the floor of the skull is explained by the early institution of treatment. The increased density in the right antrum was unrelated to the malignant disease.

wards, she developed severe pain in the right cheek, nausea and vomiting and lost 25 pounds.

Examination of the throat revealed a mass involving the right fossa of Rosenmüller, with extension into the posterior nasopharyngeal wall. A biopsy study was reported as epidermoid carcinoma Grade IV. A vertical roentgenogram of the skull showed no clean-cut area of destruction in the floor of either middle fossa. A hard lymph node measuring ¾ inches in diameter was felt beneath the angle of the right jaw.

Because of her poor general condition, port sizes were changed frequently in an effort to reduce the severity of her nausea. Doses of 300 r in air were administered daily (except Sunday) during a period of 22 days, through ports on the temples and upper right neck, of the following sizes: one 15×15 cm., three 10×10 cm. and thirteen 10×15 cm. Three doses were then given through a 7 cm. circular port laid out over the right cheek to include the right antrum. All beams were directed at the upper posterior right nasopharynx and the right middle fossa of the skull. The total air dose was 6,000 r. This treatment was given with a 220 kv. transformer, a target skin distance of 50 cm. and a Thoraeus filter made up of 0.8 mm. of tin, 0.25 mm. of copper and 1.0 mm. of aluminum.

An examination 4 days after the completion of the treatment revealed marked improvement of the soreness in the throat. The double vision and pain in the right cheek had disappeared and the nasopharyngeal tumor was no longer visible. Her nausea was completely controlled by daily intravenous injections of 5 per cent glucose in 1,000 cc. of normal salt solution.

At 6 months she was symptom-free and was gaining weight.

At 2 years, her mouth was still quite dry and the crowns of her back teeth showed the usual degeneration produced by heavy external radiation. Her dentist removed all of her teeth and prepared an excellent set of dentures.

At 25 years she felt unusually well and had none of her original symptoms. She attributes a slight slurring of her speech to the dryness of her mouth which is partially relieved by chewing gum. Her deafness in the right ear did not improve and she now wears a hearing aid. Vertical roentgenograms of the skull show no sharply defined changes.

Case III. (Fig. 3). This 22 year old woman (Mrs. A.R.C.) was admitted to the Baylor Tumor Clinic on April 20, 1937. She had complained of pain in the right eye referred to the forehead, made worse by stooping over, for about 3 years. After a swelling appeared in the right upper neck, her wisdom teeth were removed without relief. About 8 months previously she began to expectorate bloody pus and developed double vision 6 months before admission. An examination, done in another city, revealed a bleeding tumor in the right nasopharynx and, although no biopsy studies were done, she received a series of roentgen ray treatments, apparently directed to the nasopharynx during a period of 30 days. She stated that they made her very sick and that she has since lost 30 pounds.

On admission, she had a right sided internal strabismus and a marked photophobia and could not open the right eye. A neurologic examination revealed paralysis of the 3rd, 4th, 6th and part of the 5th cranial nerves. Vertical roentgenograms of the skull showed a sharply defined area of destruction, measuring about 2.5 cm. in diameter, in the right base of the skull including the foramen lacerum and the tip of the petrous portion of the temporal bone. A mass of gray tissue almost obliterated the right fossa of Rosenmüller and the findings indicated the presence of a tumor in the middle fossa of the skull.

Doses of 300 r (in air) were directed at the middle fossa on each alternate day except Sunday through opposing 10×10 cm. ports placed in each temple. The kilovoltage was 220, target skin distance 50 cm. and a Thoraeus filter was used containing 0.8 mm. of tin as its primary component.

At 3 months she felt much better but she still had a strabismus on the right side and tingling in her right cheek.

At 7 months she developed dizziness and a neurosurgeon decided that she had an extension of the tumor into the posterior fossa. The areas previously treated were shielded and doses of 300 r (in air) were given daily except Sunday through a 10×15 cm. port laid out over the posterior occiput and neck until a total dose of 3,000 r (in air) had been given in 13 days.

At 13 months she felt well except for some "infection" in the left ear and was fitted with a hearing aid.

At 14 months she had no dizziness, strabismus or double vision and had gained 30 pounds. An otolaryngologist could find no evidence of tumor in her nasopharynx.

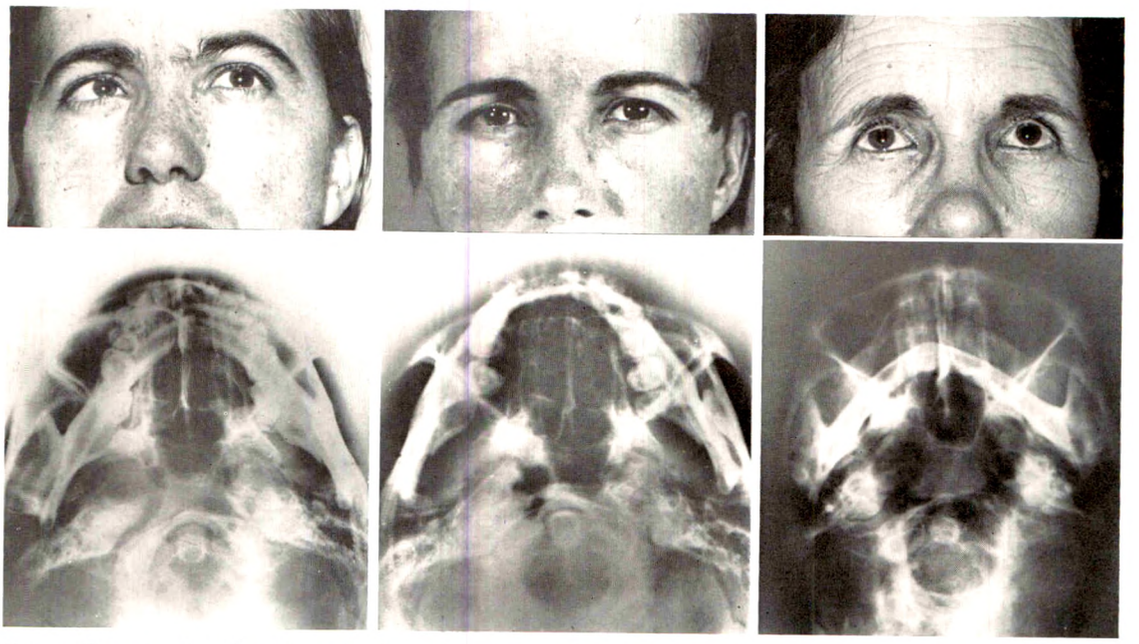


FIG. 3. Case III. Reading from the left the pairs of photographs and roentgenograms were made before treatment on April 20, 1937, and at 14 months and 29 years later. All photographs were made with the patient looking straight ahead and her eventual recovery is evident. Her slow improvement hinged on the large size of the intracranial tumor which had produced a large sharply defined area of destruction in the floor of the right middle fossa as viewed from the submental region in the first roentgenogram. Calcification in the petrous portion of the temporal bone and in the upper edge of the defect in the middle fossa can be seen in the second roentgenogram. The third roentgenogram is not made in the proper position but indicates a partial return of the calcified areas to normal.

At 29 years she feels quite well and has none of her original symptoms. However, we have noticed a slurring in her speech such as that observed in the other two patients in this series.

SEQUELAE

The temporary mucositis and radiodermatitis, together with persistent dryness of the mouth, temporary parotid swelling and persistent damage done to the crowns of the posterior teeth have been described in previous articles and will not be discussed here.

Radiotherapists are now more concerned about the temporary and permanent damage produced in the brain stem and spinal cord which must lie in the treated areas if intracranial extensions are to be controlled. In 1958 Lampe[9] reviewed the literature from 1934 to 1954 and noted a wide variation in the doses reported as safe when administered to the structures within the cranial cavity. Such variations could result from the different methods used in the calculation of depth doses or from inadequate observation periods. In our opinion, Lampe's report, covering 17 cases treated with orthovoltage surviving from 8 to 21½ years, bears much weight because of the long observation periods. His tumor doses varied from 3,000 r given in 3½ weeks to 3,600 r in 4½ weeks, 3,900 r in 4½ weeks, 3,900 r in 4½ to 5 weeks, 4,200 r in 5 to 5½ weeks and in 1 case 5,000 r given in 6 weeks. He observed no evidence of brain damage attributable to irradiation in any of these patients.

He reports the work of Boden published in 1948[1] and 1950[2] in which the maximum safe dose for large fields and orthovoltage was set down as 3,500 r in 17 days. Using Strandqvist's curves, this dose could be estimated as 3,650 r in 21 days. Since this figure is very similar to our own—and we

have observed no evidence of brain stem or spinal cord damage—we feel that it must lie within safe limits.

We have recently viewed the delivery of much larger doses to the cervical spinal cord using supervoltage machines with much concern. When this equipment first became available, some of the younger men expressed the belief that the radiation delivered to deep tissues possessed a saving effect not produced by orthovoltage. In 1960, Dynes and Smedal[7] reported the serious sequelae that occurred in their clinic in 10 cases treated with a 2 mev. machine. In all except 2, doses of 6,000 r were delivered to the spinal cord in periods varying from 49 to 68 days. In 1, doses of 2,500 r were delivered to each side of the cord in 18 days, but the fields may have overlapped so that the total dose could have been 5,000 r. In another, a dose of 1,000 r, given with 400 kv. in 15 days, was followed by 5,000 r given in 36 days with 2 mev. Of the 10 cases, 4 developed a paraplegia, 3 had a hemiplegia, and the others developed varying degrees of spasticity without paralysis. It is only fair to state that these 10 cases were picked from a series of approximately 800 with head and neck cancer treated with 2 mev. in which no such symptoms appeared.

The authors reviewed the more recent literature, including reports of serious damage to the lumbar portion of the spinal cord produced by supervoltage equipment. The dosages used ranged from 5,000 to 6,000 r and sometimes higher. The patients receiving the cord damage manifested signs of flaccid weakness with loss of reflexes in the legs, muscular atrophy and sphincteric difficulties without sensory changes.

More recently, Jones[8] described Lhermitte's sign, consisting of an electrical paresthesia felt principally in the lumbodorsal spine, arms and legs induced by flexion of the neck. This condition is usually transient and according to the author may result from 2,630 rads or more with orthovoltage and 4,680 to 5,580 rads with cobalt 60 teletherapy delivered to the spinal cord. Since we have never observed this syndrome in our cases treated with 220 kv., it will not be described in detail.

Perhaps some notice should be taken of the two symptoms common to our 3 patients followed for long periods of time after the elimination of intracranial extensions of cancer of the nasopharynx. Each of them developed a deafness requiring the use of a hearing aid and all of them have a speech defect which has not been severe enough to prevent them from communicating with others. In a previous paper reviewing 234 patients with intracranial invasion reported by 5 authors, only 1 patient had deafness secondary to the compression of the 8th nerve. It seems likely, therefore, that the loss of hearing resulted from obstruction of the eustachian tube and infection rather than from radiation damage.

We find it more difficult to explain the speech defects. Case 11 works in an office where she uses the telephone and states that she finds it difficult to make herself understood when using this instrument. She feels quite certain that this trouble is produced by a dry mouth, thick saliva and the presence of dentures. Since she is a very intelligent person, we are inclined to believe her.

CONCLUSIONS

The histories of 3 patients with internal strabismus secondary to a radiosensitive type of nasopharyngeal carcinoma with intracranial extension who are well with straightened eyes and no evidence of the disease at the end of 9½, 25 and 29 years after radiation therapy are reported, because it has been found very difficult to discover similar results either in this country or abroad. Nasopharyngeal cancer seems to appear more frequently in Southern China, Hong Kong and Taiwan than in other parts of the world, but no long time cures have been reported in these areas. Two similar good results have been discovered in Brasil, 1 in New York and 1 in Toronto.

Evidence is presented indicating that the old time-tried orthovoltage roentgen ray techniques have produced good results, without incurring the risk of serious sequelae in the brain stem and spinal cord reported following the more intensive irradiation of the deep structures with supervoltage roentgen ray machines and the cobalt 60 teletherapy units.

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A WATER-JET DEVICE FOR SUPPORTIVE CARE IN ORAL CANCER*

By MALCOLM A. BAGSHAW, M.D.†
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SUPPORTIVE care of the oral tissues during the treatment of cancer of the oral cavity and pharynx is well recognized by radiotherapists as an important adjunct in the radiotherapy of primary carcinomas in these regions. The oral douche by gravity lavage and cleansing of the oral and pharyngeal tissues with a power spray are treatment aids in common use. It is impractical for a patient to utilize a power spray on his own and oral lavage is often of insufficient power to provide adequate debridement of infected, necrotic tissue. A pulsating water pressure device known to the dental profession*[1] has been in use in our department for 3 years for the maintenance of oral hygiene both during and after radiotherapy (Fig. 1). This device consists of a reservoir which may be filled with 1 per cent hydrogen peroxide or other irrigating solutions and a pump which delivers a pulsating jet through a small plastic nozzle. According to the manufacturer, the jet pulses 1,200 times per minute. The pressure of the jet may be adjusted over a considerable range and the patient may be taught to use the device either at home or in the hospital.

In our ongoing study of the treatment of advanced carcinoma of the head and neck by combined therapy with intra-arterial chemotherapeutic agents and irradiation, we have been impressed by the contribution made by this device in maintaining satisfactory oral hygiene during therapy. Objectively, necrotic debris are mobilized, radiation reaction is minimized and circulation to the tumor bed seems improved. Subjectively, the patient's discomfort is significantly minimized. Routine lavage 4 or 5 times daily with the pulsating jet of irrigating solution has become an indispensable adjunct in our radiotherapy of oral cancer.

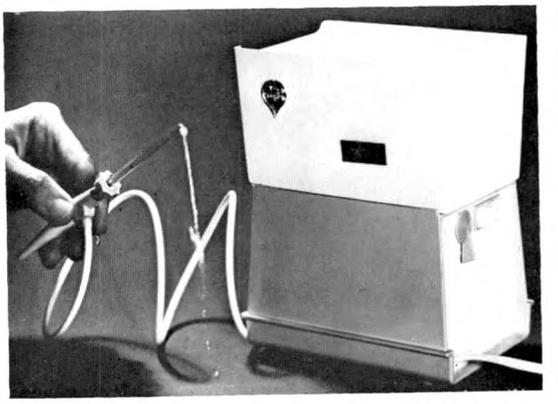


FIG. 1. Photograph of water-jet device for supportive care in oral cancer.

SUMMARY

A new type of device for oral irrigation in cases of oral cancer is described. This water-jet device has been used for more than 3 years and has proved to be a valuable adjunct in the treatment of these cases.

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* Water pik produced by Aquatek Corporation, Ft. Collins, Colorado.

* Radiotherapy research, supported by U.S.P.H.S. Grant number CA 5008.
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VOL. 99, NO. 4

HODGKIN'S DISEASE*

TUMOR LETHAL DOSE AND ISO-EFFECT RECOVERY CURVE

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THIS clinical radiobiologic study was designed to construct an iso-effect recovery curve for Hodgkin's disease by employing the "minimum corroborated tumor lethal dose technique" previously described by us in time-dose studies based on recurrent breast cancer[3] and mycosis fungoides.[4]

From a total population of 350 patients, we selected 123 previously untreated patients, because they offered the types of data useful for this study. The criteria for selection were: each patient had to have multiple tumors (Table I) whose response to treatment and rate of shrinkage were recorded graphically (Fig. 6), and the follow-up period had to be at least 2 years. Forty were "lifetime" patients, *i.e.*, the authors gave all the treatments from onset of disease to death or survival to date, the longest being 16 years. The remaining 83 "transient" cases were treated for more than 2 years and then they moved elsewhere.

From this population, 484 dose points were assembled in a scatter diagram (Fig. 1). The 327 solid dots represent the successful doses which produced local control for more than 2 years. A single lymph node region, such as the axilla which might contain 5 lymph nodes, was recorded as a single dose point. Open circles represent 157 failures, *i.e.*, residuum or recurrence in less than 2 years.

All doses referred to in this paper are tumor doses expressed in rads without a relative biologic effect (RBE) correction.

The crude dose points shown in Figure 1 were too widely dispersed for a meaningful statistical analysis. Therefore, the "minimum corroborated tumor lethal dose technique"[3] was employed.

THE MINIMUM CORROBORATED TUMOR LETHAL DOSE TECHNIQUE

This technique was designed to avoid the error of previously published iso-effect curves,[1,10] which were based upon all successful doses that destroyed a tumor without causing radionecrosis. Many of these tumor doses were excessive. They were haphazardly distributed over a wide range and therefore distorted the resultant iso-effect curves. The dose diagram of Case 1 demonstrates how the corroborated dose technique reduced this error (Fig. 2). Although there were 14 successful dose points in this patient, only the 7 smallest effective doses (large solid dots) which lay in a zone close to "failures" were used. They were designated as "minimum corroborated tu-

TABLE I
DERIVATION OF CORROBORATED DOSE POINTS

No. of Patients	Total No. of Lymph Node Regions in Each Patient	No. of Corroborated Dose Points Derived from Each Patient
1	10	6
1	22	5
1	6	4
1	4	3
7	14, 13, 11, 8 7, 5, 3	2
9	13, 7, 7, 5, 5 4, 3, 2, 2	1
Total 20	151	41

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
From the Radiation Therapy Division of the Department of Radiology, New York University Schools of Medicine, New York, New York.

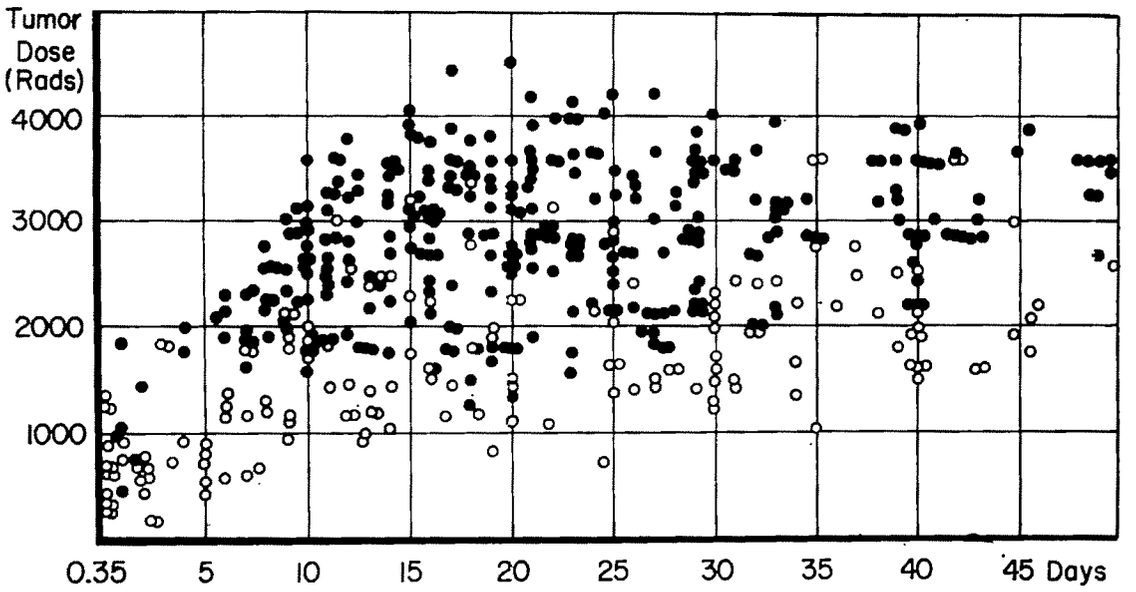


Fig. 1. Two year results of different time-doses given to 484 Hodgkin's disease lymph node regions. Solid dots signify local control; circles signify failures.

mor lethal doses." A freehand iso-effect curve was drawn through these corroborated dose points.

Five additional patients are illustrated in Figure 3, *A–E*. Figure 3*A* yielded only 2 corroborated dose points, but provided data for the first 2 weeks. In Figure 3*B*, note that the slope of the freehand iso-effect curve is markedly different from that in the previous case, and at a higher dose level.

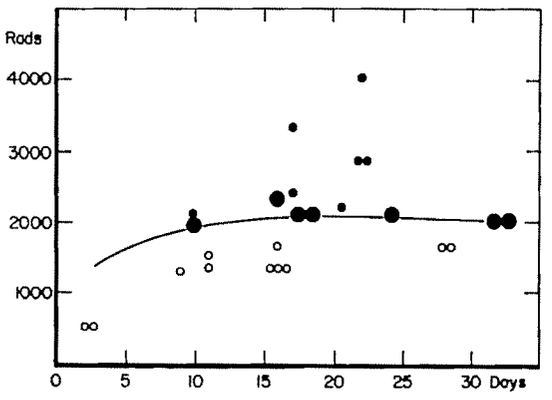


Fig. 2. Case 1. Scatter diagram of doses given to 25 lesions in the same patient. Circles represent failures; solid dots are successes. The small dots represent given doses which were effective but probably excessive in amount. The large dots represent "minimum corroborated tumor lethal doses," because they lie close to the zone of inadequate dosage. The iso-effect curve is based on the latter points and is drawn freehand.

Analysis of Data and Construction of Iso-Effect Curves

The individual iso-effect curves of 25 patients were drawn freehand because no patient had enough dose points to support a calculated curve (Fig. 4). They occupy a zone which delineates the range of radiosensitivity of a representative spectrum of Hodgkin's lymph nodes. The variation in slope of the individual curves suggests that there may be a different recovery factor for each patient's tumors, due to the multiple factors influencing the behavior of the disease.

The 41 corroborated dose-points from 20 patients (Table 1), similar to those illustrated in Figures 2 and 3, *A–E* were assembled in Figure 5. An average regression curve was calculated with the aid of a computer. This curve has some validity because it was based on minimum corroborated tumor lethal doses. The slope of the curve, *i.e.* recovery factor, is 0.25. The 95 per cent confidence limits are 0.13 to 0.36. The significance of the slope will be discussed later.

This time-dose curve is of radiobiologic interest only. The slope seems reasonably correct. For clinical purposes, the doses should follow a parallel curve at a higher dose level (Fig. 11).

The iso-effect curve of "slow but complete shrinkage" (Zone C in Fig. 6) was compared with that of the "minimum corroborated tumor lethal dose" curve. In our previous study of recurrent breast cancer,[3] the 2 curves were similar, as would be expected since in both instances minimal tumor lethal doses were employed. In this Hodgkin's disease study, the 2 curves were similar but the confidence limits were too broad and overlapped each other so that no further deductions could be drawn from this comparison.

ANALYSIS OF SHRINKAGE CURVES

The volume of each lymph node was plotted at twice-weekly intervals and recorded as a shrinkage curve (Fig. 6). The shrinkage curve of an extremely radio-

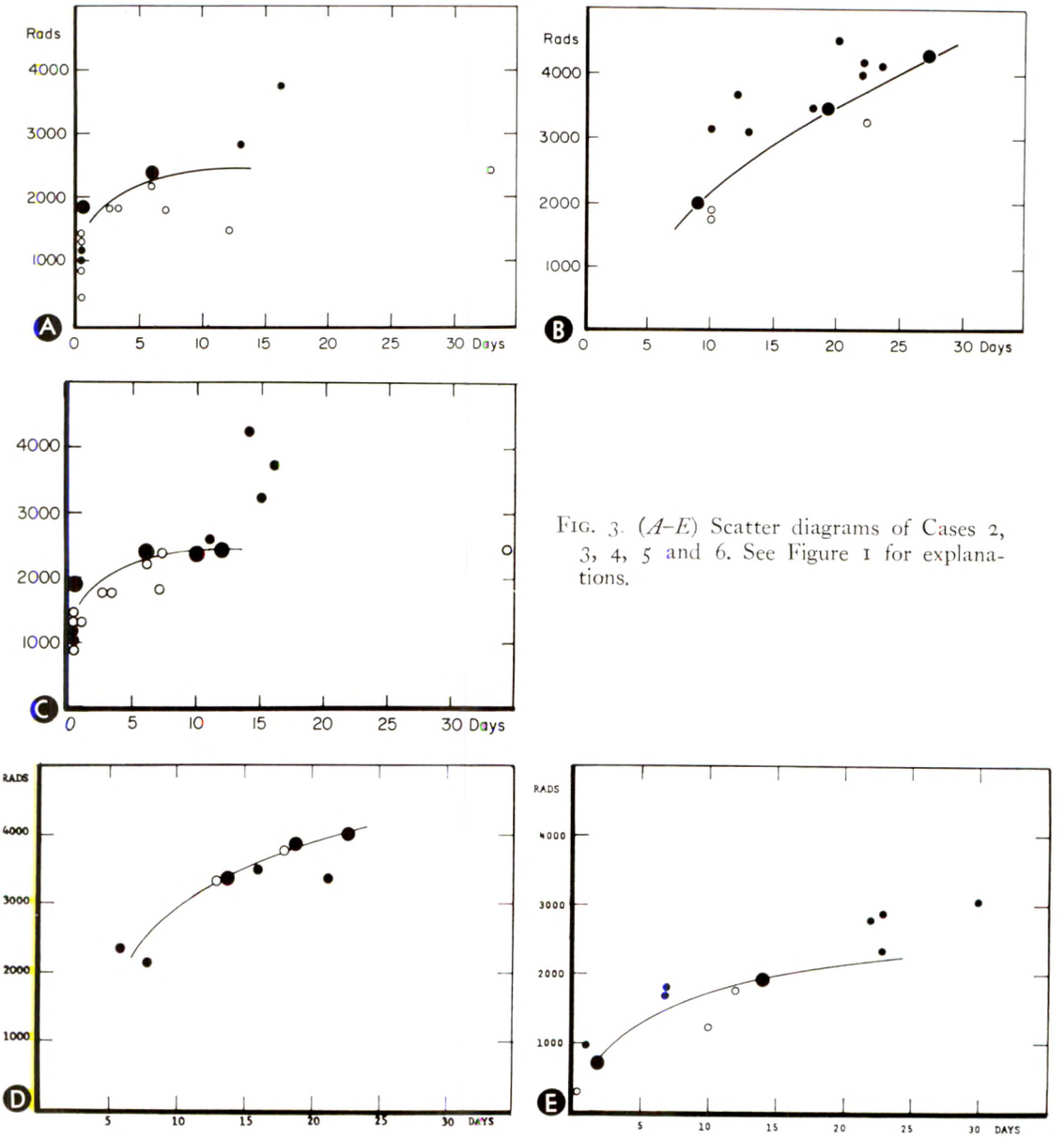


FIG. 3. (*A–E*) Scatter diagrams of Cases 2, 3, 4, 5 and 6. See Figure 1 for explanations.

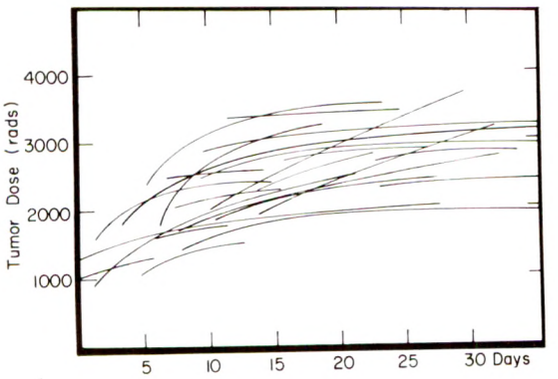


Fig. 4. Individual iso-effect curves of 25 patients. Note variations in slope, dose levels, and shape of curves. Nevertheless, they occupy a zone which delineates the range of radiosensitivity of a representative spectrum of Hodgkin's disease lymph nodes.

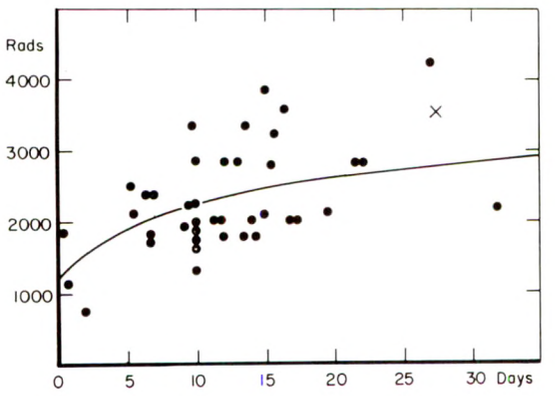


Fig. 5. Corroborated minimal tumor lethal dose. Forty-one "corroborated" dose points from 20 patients (See Table 1). The curve, fitted with the aid of a computer, has a slope (or recovery factor) of 0.25.

sensitive tumor would lie in Zones A and B. The shrinkage curve of a less sensitive tumor would lie in Zone C, which depicts "slow but ultimately complete shrinkage." This is a threshold effect based on the radiobiologic phenomenon of tumor *shrinkage*. It is analogous to the "minimum corroborated tumor lethal dose" which is a threshold effect based on *dose*.

The shrinkage curves of the lymph nodes in a patient whose lesions are radiosensitive are shown in Figure 7. It has in the past been our impression that this feature of radiosensitivity tended to remain const for each successive lymph node through the entire course of a patient's dise Similarly, when the early lesions in a tient were radioresistant and their shr age curves lay in Zones C or D, subsequ lesions tended to be radioresistant (Fig To study this feature further, the shrink curve data of 31 "life-time" patients v subjected to detailed computer analysi

Contrary to our previous expectatior only half the cases did the rate of shrink follow a consistent pattern of either ra

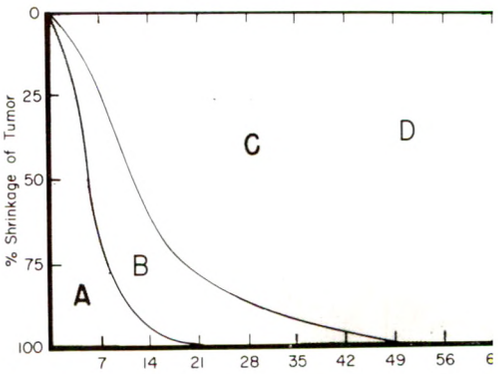


Fig. 6. Zones for classifying tumor shrinkage cu The shrinkage curves of an extremely radios tive tumor would fall into Zone A or B; "slov complete shrinkage" in Zone C; failures in Zo The two solid lines depict hypothetical shrin curves.

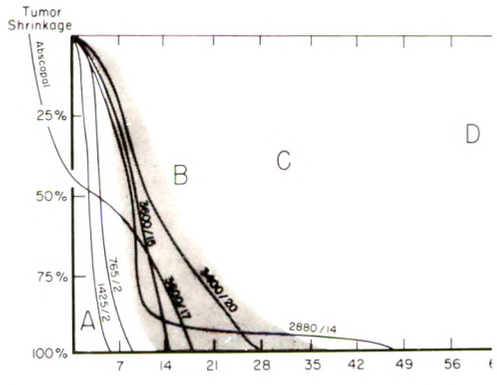


Fig. 7. Shrinkage curves of 6 lymph nodes in tient, wherein all lesions were very radiosen and their curves lie in Zones A and B. Note the lymph nodes shrinking most rapidly rec the smallest doses. Note also the marked abs effect on 1 lymph node.

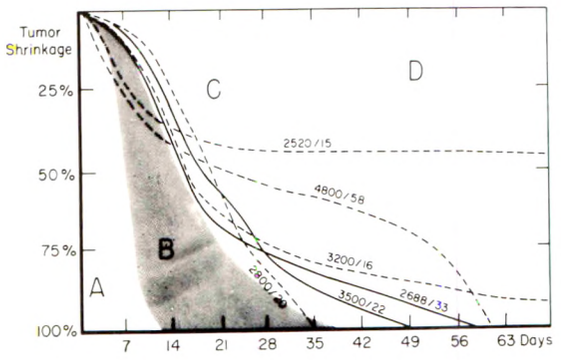


FIG. 8. Shrinkage curves of 6 lymph nodes in another patient, wherein all the lesions were radioresistant.

sensitivity or radioresistance. In the other half, the response was not consistent. Therefore the biologic index, *i.e.* rate of shrinkage, could not be used to evaluate the effect of a stated dose.[11]

RBE FACTOR: 200 KEV. VS. 2 MV.

In this study, doses were calibrated in roentgens and then converted to rads. The RBE factor was not employed when normalizing orthovoltage and supervoltage doses because of the uncertainty as to the magnitude of the correction factor.[7]

The only data which yielded some information concerning this question were a comparison of time-dose points which produced 2 year arrests of "large" tumors, *i.e.*, greater than 5 cm. diameter. They comprised mostly mediastinal and abdominal tumors. The supervoltage curve had a statistically significant slope of 0.3 with a 95 per cent confidence interval ranging from 0.1 to 0.5. The orthovoltage curve had a slope of 0.2, but due to the paucity of data, this estimate was not considered statistically significant, *i.e.*, it could be zero (Fig. 9). Therefore, the data from this study could not be used to determine the magnitude of the RBE factor.

However, from inspection of the distribution of the dose points in Figure 9, the data imply that, when supervoltage irradiation is used in order to achieve the same clinical response, larger rad doses must be given than with orthovoltage roentgen rays.

THE RELATION OF DOSE TO LOCAL CONTROL

Figure 10 is a scatter diagram of 176 doses in 52 patients which produced local control for at least 5 years. It illustrates the wide range of dosage that can be successfully employed in Hodgkin's disease. The solid line (A) is a calculated average regression curve which is useful radiobiologically but less so clinically. The X, representing a tumor dose of 3,500 rads in 28 days, has been empirically selected by a group of experienced radiotherapists (The Committee for Radiation Therapy Studies) for use in a clinical trial based on Hodgkin's disease. A curve drawn through the X and parallel to Curve A, would delineate a clinically useful dose level. It is not unexpected that Curve A, being an average curve, is at essentially the same dose level as the minimum corroborated tumor lethal dose curve. Doses along the latter 2 curves would produce a 70 per cent probability of 5 year local control. Many 5 year local controls were achieved with small doses.

The per cent probability of local control for a period of more than 2 years, using doses in graded levels, is illustrated in Figure 11, which is similar to Figure 1. The scatter diagram is subdivided into 6 zones by drawing parameters with the same slope

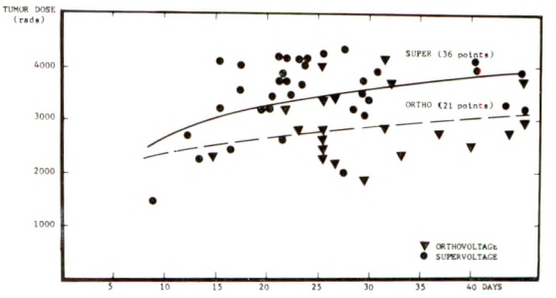


FIG. 9. Comparison of supervoltage doses with orthovoltage doses which produced 2 year arrest of large tumors. The relative relation of the 2 regression curves is not statistically significant because of the overlapping of their confidence limits. Nevertheless, inspection of the dose points as well as the 2 curves leaves the implication that, when supervoltage irradiation is used to achieve the same clinical response, larger rad doses must be given than with orthovoltage roentgen rays.

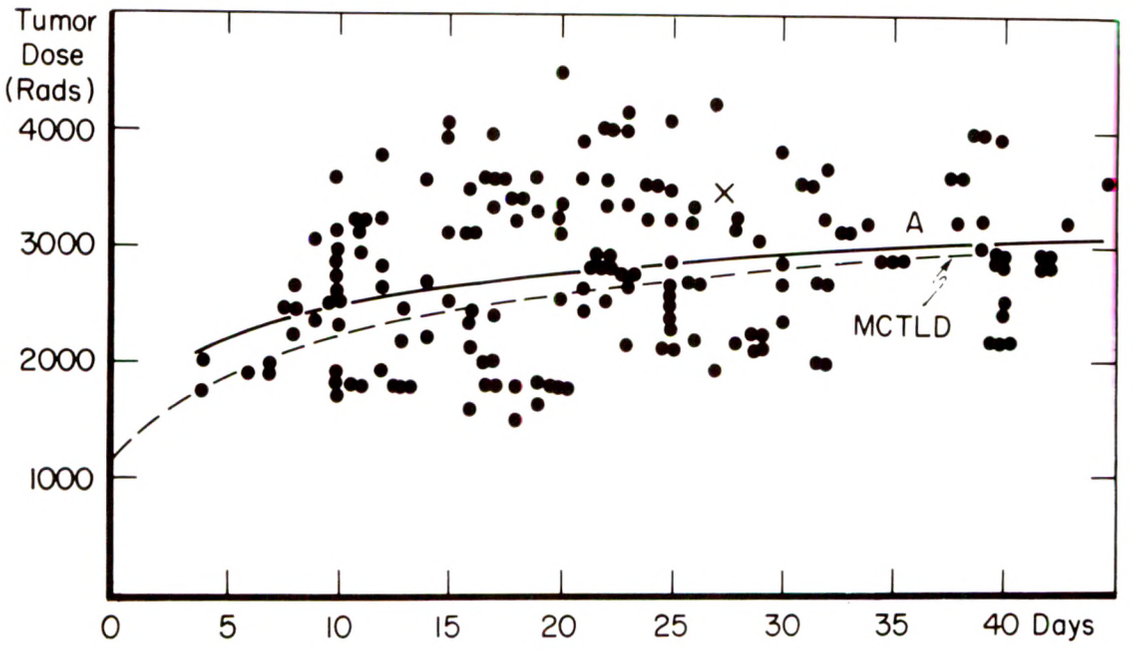


Fig. 10. Five year arrests—all tumors. These 176 doses in 52 patients produced local control for more than 5 years. The calculated average regression curve (A) is essentially similar to the curve for "minimum corroborated tumor lethal dose" (MCTLD). See text for explanation of X.

as our radiobiologic standard, *i.e.*, the minimum corroborated tumor lethal dose curve, normalized to an over-all 28 day fractionation.

The data from the scatter diagram (Fig. 11) are tabulated in Table II. Analysis of doses producing local control for 2 to 5 years shows graded results in relation to

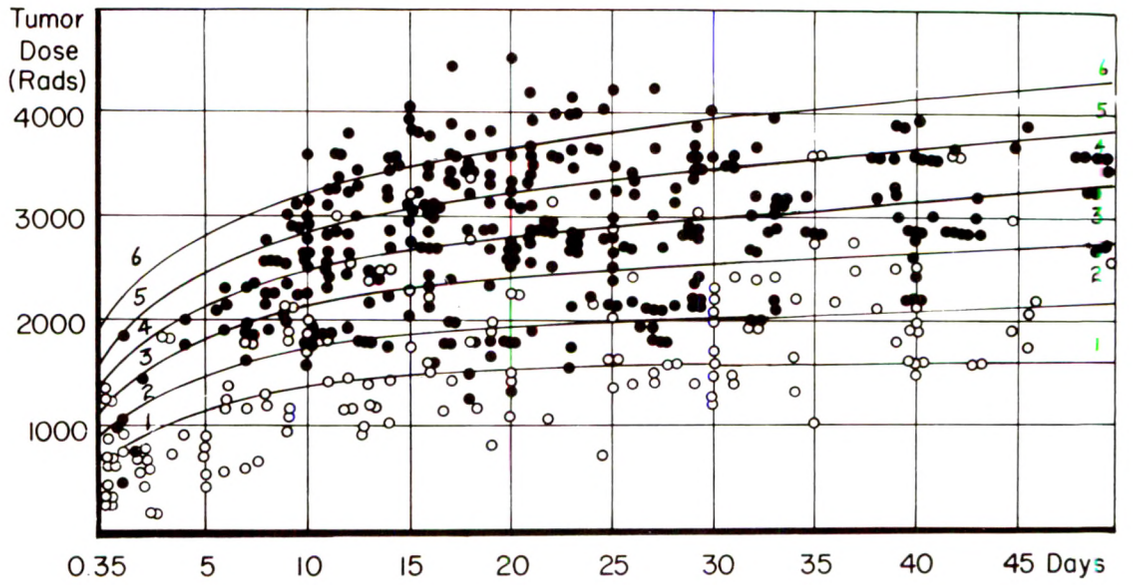


Fig. 11. Hodgkin's disease. Total data—484 doses. The data shown in Figure 1 are here divided into 6 dose levels by lines whose slope parallels the MCTLD in Figures 5 and 10. See Table II for degree of local control produced by each dose level.

TABLE II

RELATION OF DOSE TO LOCAL CONTROL

Equivalent Rad Doses in 28 Days	No. of Lymph Node Regions	Local Control for 2–5 Years		No. of Lymph Node Regions	Local Control for More Than 5 Years	
		No.	Per Cent		No.	Per Cent
1,500–1,999	60	21	35	49	10	20
2,000–2,499	74	42	57	65	29	45
2,500–2,999	94	76	81	65	44	68
3,000–3,499	84	73	87	50	36	72
3,500–3,999	54	50	93	19	13	68
Over 4,000	27	26	96			
Totals	393	288	73	248	132	53

graded doses. For example, that dose range which encompasses 2,000 to 2,499 rads in 28 days produces 57 per cent local control, whereas 4,000 rads in 28 days produce 96 per cent local control.

On the other hand, when analyzing local control for 5 years, doses higher than 3,000 rads did not appear to increase the probability of success. Admittedly, the relative paucity of data weakens this deduction, but still suggests that factors other than dose may influence long-term local control.

These considerations do not invalidate the conclusion that an optimum tumor dose to be employed routinely in Hodgkin's disease should lie within Zone 5 (Fig. 11), which encompasses the dose, 3,500 rads in 28 days. This large-dose technique has been employed by us in cases of Hodgkin's disease for the past 24 years not only for known tumor but also for prophylactic irradiation of uninvolved regions.[5]

THE CALCULATED RECOVERY FACTOR

A calculated recovery factor for different tumors has been derived by several authors.[1,3,4,8,9,10] It represents the slope of a curve on a log-log graph. The data have been assembled in Table III. Slopes higher than 0.20 represent significant recovery. However, there are many inconsistencies due to the difficulty of collecting statistically valid data in human beings. The recovery curves for the 2 cases of mycosis fungoides[4] are a good example of 2 similar

TABLE III

CALCULATED RECOVERY FACTOR FOR VARIOUS TISSUES

Author	Tissue	Recovery Factor
Cohen[1]	Breast cancer	0.34
Cohen[1]	Skin (erythema)	0.33
Quimby and MacComb[8]	Skin (erythema)	0.22
Strandqvist[10]	Skin cancer	0.31
Scott and Brizel[9]	Hodgkin's disease (ortho-volt)	0.33
Scott and Brizel[9]	Hodgkin's disease (super-volt)	0.29
Friedman and Pearlman[3]	Recurrent breast cancer	0.25
Friedman and Pearlman[4]	Mycosis fungoides	0.12
Friedman and Pearlman[4]	Mycosis fungoides	0.40
Friedman and Pearlman Present series	Hodgkin's disease	0.25

extremely radiosensitive lesions, wherein minimal recovery effects were expected. These 2 cases are supported by more observations than any other in Table III. Yet the slopes of the 2 curves (0.12 and 0.40) were widely disparate. Scott and Brizel[9] reported 2 curves for Hodgkin's disease with slopes of 0.33 (orthovoltage radiation, based on 75 points) and 0.29 (supervoltage radiation, based on 13 points). Yet the more extensively documented curve shown in Figure 5 has a slope of 0.25.

Despite, these disparities it is useful to continue collecting recovery data of this type.

EQUIVALENT SINGLE DOSE (ESD)

When describing the lethal dose of a particular tumor, it may be convenient to symbolize that dose in terms of an equivalent dose given in a single exposure. This is obtained by extrapolating the tumor lethal dose curve back to the ordinate representing a single exposure.[2,3] The authors doubt that the ESD is appropriate for clinical purposes, as it lacks the normal-tissue-sparing effects achieved by fractionation. However the ESD may be a useful radio biologic symbol.

CONCLUSIONS

1. In a study of time-dose relationships based on Hodgkin's disease, an iso-effect recovery curve was calculated using the "minimum corroborated tumor lethal dose" tactic. Its slope of 0.25 suggested that Hodgkin's disease tissue was capable of recovery from radiation effects, and that its rate of recovery more closely resembled that of carcinoma than a radiosensitive lymphoma such as mycosis fungoides.

2. In one-half of cases of Hodgkin's disease, all the lesions in a single patient responded consistently to irradiation, being either radiosensitive or radioresistant. However, among the remaining patients there was a mixed pattern of rate of tumor shrinkage. This invalidated the use of "rate of shrinkage" for clinical or radiobiologic purposes.

3. Analysis of the relation of dose to local control corroborates our 24 year old empirical clinical technique of employing radical irradiation to involved and uninvolved areas, using tumor doses of 3,500 to 4,000 rads in approximately 28 days. This had yielded from 93 to 96 per cent local control.

4. The "equivalent single dose" for Hodgkin's disease is 1,750 rads when the aim of dosage is local control, and 1,178 rads for a "minimum corroborated tumor lethal dose."

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HEPATIC GAMMASCANNING AS AN AID IN THE MANAGEMENT OF PATIENTS WITH MALIGNANT LYMPHOMAS*

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ACCURATE clinical assessment of the liver is a challenge to the clinician treating patients with malignant lymphomas, inasmuch as from one-half to two-thirds of the patients suffering from malignant lymphoma will present involvement of the liver by the neoplastic process at some period during their lifetime. Of 316 patients with Hodgkin's disease, 35 per cent presented hepatic involvement.[8] Of 567 patients with lymphosarcoma, 56 per cent were found to have clinical hepatic involvement.[7] Other investigators have reported a necropsy incidence of hepatic involvement by Hodgkin's disease varying from 38 to 66 per cent,[4,14] and a necropsy incidence of hepatic involvement by patients with lymphosarcoma varying from 10 to 51.3 per cent.[12]

AIDS IN THE DIAGNOSIS OF HEPATIC LYMPHOMA

When jaundice occurs in a patient with malignant lymphoma, adroit clinical diagnostic acumen is necessary since the etiologic factor may be either intrahepatic lymphomatous disease, extrahepatic lymphomatous disease producing obstructive jaundice, or a combination of these conditions. In addition, all of the known nonlymphomatous diseases involving the liver, such as cirrhosis and hepatitis, or involving the biliary system, such as choledocholithiasis, as well as hemolytic anemia and metastases from other primary cancers must be included in the differential diagnosis.

In 159 patients with lymphosarcoma presenting jaundice, an obstruction at the porta hepatis, observed either on exploration or at necropsy, was found to be the cause of the jaundice in 11.3 per cent of the patients.[12] In a series of 57 necropsied patients with Hodgkin's disease and jaundice, liver involvement by Hodgkin's disease was present in 70.2 per cent. There was no satisfactory explanation for the jaundice in 17 per cent; however, hemolytic anemia was present in 5.2 per cent, extrahepatic bile-duct obstruction due to tumor in 3.5 per cent, hepatitis in 3.5 per cent, choledocholithiasis in 1.8 per cent, and cirrhosis in 1.8 per cent.[5]

Hepatomegalia is not necessarily diagnostic of hepatic lymphomatous disease in patients with known malignant lymphomas. Associated splenomegalia may be a helpful clue.[4]

Liver function tests are of limited value in establishing the etiologic nature of the liver pathology. High elevations of the serum glutamic oxalacetic transaminase (SGOT) are useful to establish the presence of hepatitis. Only slight or moderate elevations in the SGOT may reflect intrahepatic lymphomatous involvement, extrahepatic biliary obstruction (both lymphomatous and nonlymphomatous), or other liver disease processes such as postnecrotic cirrhosis, portal cirrhosis, fatty metamorphosis, passive congestion, amyloidosis, and abscesses.[6,9]

Liver biopsies are useful but their accuracy varies an estimated 70 to 78 per cent in patients with metastases to the liver with associated suggestive biochemical and physical findings.[3,11,15] In many patients with malignant lymphomas a liver biopsy is often contraindicated owing to an as-

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sociated thrombocytopenia and altered bleeding and clotting times as well as hypoprothrombinemia unresponsive to vitamin K.

VALUE OF HEPATIC GAMMASCANNING

Hepatic gammascanning, using radioactive tracers to demonstrate space-occupying defects in the liver, was demonstrated by Stirrett, Yuhl, and Cassen[13] in 1954. Since then, this procedure has been employed to visualize not only the space-occupying lesions of primary and metastatic cancers, cysts, and abscesses, but to establish variations in the normal contour, size, and position of the liver and to identify diffuse parenchymatous diseases, such as hepatitis, cirrhosis, and diffuse hepatic involvement by malignant lymphoma.

Nagler, Bender, and Blau[10] have reported an 83 per cent accuracy in 402 patients with positive scans and an 88 per cent accuracy in 146 patients with negative scans. The causes of the false positive scans included: cirrhosis, fatty metamorphosis, liver abscesses, liver necrosis and fatty metamorphosis, and normal liver architecture.

METHOD

Since October, 1963, photoscanning of the liver in selected patients with malignant lymphoma was performed as an adjunctive measure to aid in their clinical management. All of the patients had a tissue diagnosis of either Hodgkin's disease (granuloma, sarcoma, or undifferentiated Hodgkin's disease), or lymphosarcoma (small cell variety or reticulum cell sarcoma).

Hepatic gammascanning was performed using I^{131} rose bengal. It has been demonstrated that the parenchymal liver cells selectively absorb and excrete I^{131} rose bengal.[2] Consequently, parenchymal cell function is reflected by the photoscan performed 20 to 25 minutes following the intravenous injection of 250 to 300 microcuries of I^{131} rose bengal.

The physical half-life of I^{131} rose bengal is 8 days. It is estimated that an adult given 200 microcuries of radioactive I^{131} will receive a total body radiation exposure of 0.04 to 0.12 r in beta rays and 0.027 to 0.082 r gamma ray irradiation. The hepatic irradiation is believed to be about 0.5 r, a level considered perfectly safe.[1]

A commercially available Baird-Atomic (CS-500) medical scanner was utilized. A dot scan is printed on heat-sensitive teledeltos paper, and simultaneously a photoscan is projected on a 14 by 17 inch film (Blue Brand, Eastman Kodak).

All scans were performed under the same conditions: high voltage, 850 volts; speed, 20 inches per minute; line spacing, 5/32 inches; time constant, 0.1 second; density, 68; a 37-hole tungsten focusing collimator; aperture (light mask), 0.125 inch square. For the I^{131} rose bengal scan, the lower and upper discriminators were set from 310 to 410 to straddle the 364 kev. peak of I^{131}. The dot scans were marked with skeletal reference points including the nipple areas, xyphoid process, and lower rib margin, and transferred to the developed photoscan in wax pencil.

MATERIALS AND RESULTS

HODGKIN'S DISEASE

Sixteen hepatic photoscans have been done in 10 patients with Stage II (regional) or Stage III (generalized) Hodgkin's disease (Table 1). One of these patients was slightly jaundiced.

The majority of the patients having positive scans showed a diffuse, erratic pickup indicative of generalized parenchymal involvement. The minority had only nodular involvement. An occasional patient had both a diffuse and a nodular pattern. None of the patients in this small series presented evidence of obstruction of the porta hepatis, as described for certain patients with metastatic cancer.[2] These scan patterns compare favorably with the incidence of reported lesions found at necropsy in a series of 112 patients with Hodgkin's disease: diffuse infiltration was found in 86.5 per cent of the 74 patients with hepatic involvement, nodular lesions in 10.8 per cent, and a mixture of diffuse and nodular lesions in 2.7 per cent.[4]

Four patients with Stage II Hodgkin's disease have shown normal liver scans and no clinical evidence of activity. In 2 of these patients, because of obesity, it was impossible accurately to palpate the edge of the liver.

Diffuse Parenchymatous Infiltration of the Liver by Hodgkin's Disease. Inasmuch as most of the hepatic involvement from Hodgkin's disease is manifested by a diffuse parenchymatous infiltration of the neoplastic process, hepatic scans may reveal this diffuse infiltration as an irregularity in the concentration of the I^{131} rose bengal. At times, hepatomegalia may be present to assist in the diagnosis. However, diffuse parenchymatous infiltration produces a scan which is the same as that produced by diffuse nonlymphomatous hepatic diseases such as hepatitis, fatty degeneration, and the early stages of cirrhosis. In this instance, hepatic function tests may assist in the interpretation of the results as observed on the scan. The patient with either hepatitis or fatty degeneration will show a greater incidence of abnormality in many more of the liver function tests than will the patient with diffuse lymphomatous infiltration. The tests which tend to be abnormal in patients with lymphoma are (1) the serum alkaline phosphatase, (2) the serum glutamic oxalacetic transaminase (SGOT), and (3) the bromsulphalein dye retention test.

The foregoing observations are exemplified by the scans performed on some of our patients. Figure 1*A* represents the hepatic photoscan of a 47 year old male with Hodgkin's disease. This demonstrates a mild hepatomegalia and a splotchy pickup of the I^{131} rose bengal, the result of defective clearance of the isotope by the liver from the blood stream. This patient manifested a 40 per cent clearance of the isotope in 30

TABLE I

LIVER SCANS IN 10 PATIENTS WITH HODGKIN'S DISEASE

Patient No.	Age (yr.)	Sex	Scan Pattern		Necropsy	Comment
			Initial	Repeat		
1	47	M	Diffuse enlargement October, 1963	Smaller, almost normal July, 1964	None	Irradiation to liver reduced its size
2	26	M	Diffuse enlargement April, 1965	No significant change September, 1965	Diffuse parenchymal infiltration	Unresponsive to treatment
3	22	F	Diffuse nodular enlargement		Diffuse nodular enlargement	Liver smaller after irradiation, pain relieved
4	24	M	Diffuse enlargement December, 1965	No significant change March, 1966	Alive	Disease controlled with prednisone, Velban
5	45	M	Diffuse erratic enlargement, December, 1965	No significant change March, 1966	Alive	Disease controlled with prednisone, Velban
6	46	F	Diffuse erratic enlargement, October, 1964	No significant change, 2 scans, November, 1965, April, 1966	Alive	Disease controlled with prednisone, Velban
7	16	F	Normal		Alive	Living and well after roentgen therapy to regional disease
8	34	M	Normal		Alive	Living and well after roentgen therapy to regional disease
9	36	F	Normal		Alive	Living and well after roentgen therapy to regional disease
10	32	F	Normal		Alive	Living and well after roentgen therapy to regional disease

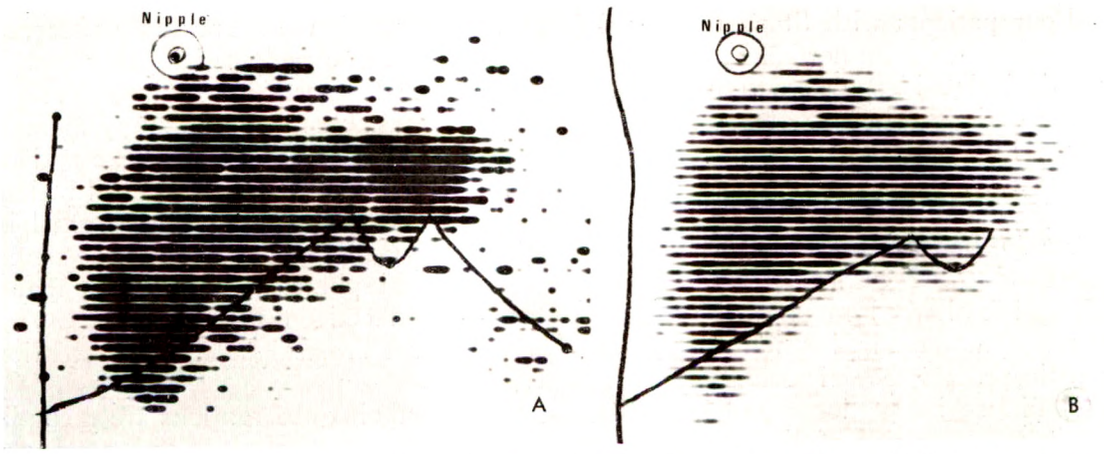


Fig. 1. (*A*) Hepatic photoscan of a 47 year old male with Hodgkin's disease. Note mild hepatomegalia and splotchy pickup of I^{131} rose bengal owing to defective clearance of isotopic dye by the liver from the blood stream (40 per cent clearance in 30 minutes; 50 per cent considered normal). The perihepatic discoloration is considered to be due to I^{131} rose bengal within the circulation. (*B*) Hepatic photoscan taken 2 weeks after the administration of 2,000 rads to the liver in 3 weeks by an orthovoltage generator. Note normal appearance of liver with more orderly pickup of the dye. Clearance of I^{131} rose bengal from the circulation has improved (60 per cent in 30 minutes). The liver is somewhat smaller.

minutes, whereas we consider a 50 per cent clearance in 30 minutes to be the minimum of normal. The perihepatic discoloration noted throughout the scan is considered to be the result of retention of I^{131} rose bengal within the circulation. Although there was no clear-cut evidence of diffuse infiltration by Hodgkin's disease, the data were considered sufficient to warrant therapy. The liver function tests were within the normal range. The patient was treated by orthovoltage irradiation, receiving 2,000 rads to the liver in 3 weeks followed by marked symptomatic improvement. A repeat hepatic scan (Fig. 1*B*), taken 2 weeks after the completion of the external irradiation, revealed moderate diminution in the size of the liver, but, more important, a more even pickup of the I^{131} rose bengal was evident.

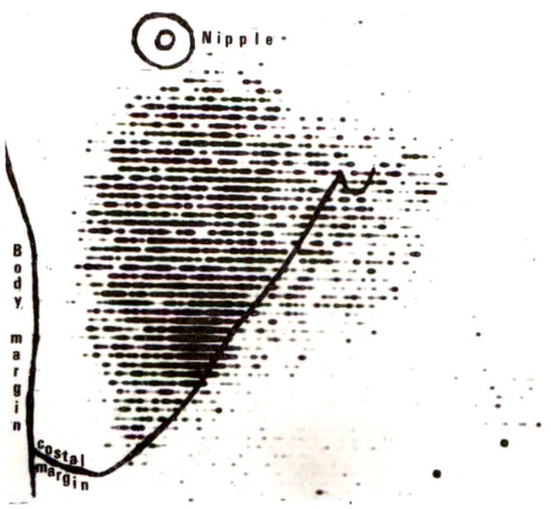


Fig. 2. Hepatic photoscan in a 26 year old male. A diagnosis of diffuse parenchymatous involvement by Hodgkin's disease was made on the basis of the scan which showed an erratic concentration of the I^{131} rose bengal by the liver and mild hepatomegalia. External irradiation and chemotherapy were administered. Necropsy confirmed the diagnosis made on the basis of the scan.

Figure 2 is the hepatic photoscan of a 26 year old male. The liver function tests were essentially normal. However, the scan revealed mild hepatomegalia and an erratic concentration of the I^{131} rose bengal, particularly in the region of the left lobe. A diagnosis of hepatic involvement by Hodgkin's disease was made on the basis of the scan and, accordingly, the patient was treated by cancer chemotherapy and external irradiation to the liver. After the administration of 1,000 rads with the orthovoltage generator in a period of 2 weeks, the treatment was discontinued because the patient showed signs of deteriora-

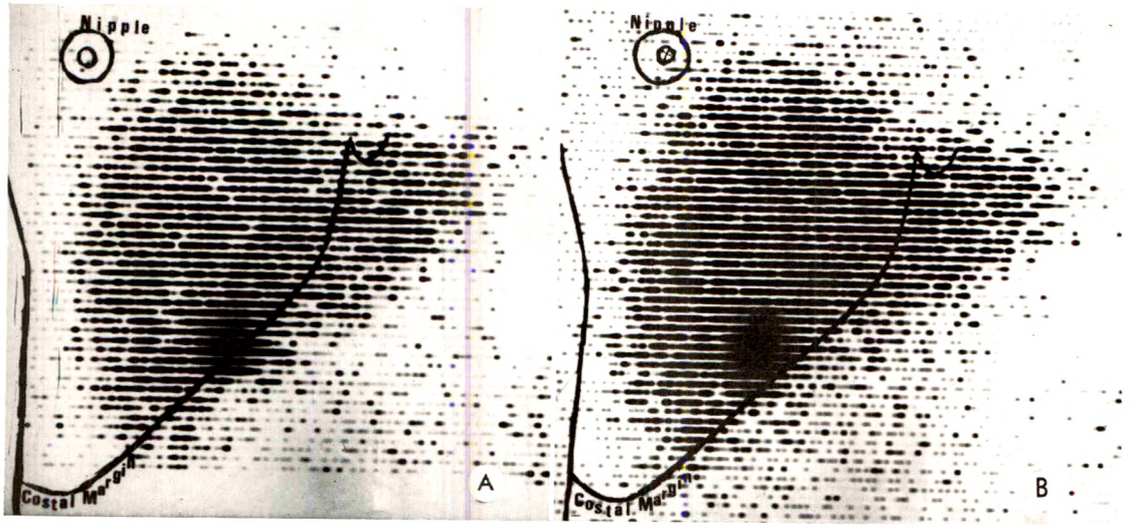


Fig. 3. (*A*) Hepatic photoscan in a 24 year old male with Hodgkin's disease, showing diffuse hepatic enlargement. (*B*) No significant change in repeat scan taken 3 months later. Treated by intravenous prednisone and Velban, with control of pruritus and fever and a decrease in the serum alkaline phosphatase level.

tion. He expired 1 month later, and postmortem examination revealed a diffuse infiltration of the liver by Hodgkin's disease, confirming the diagnosis as established by the scan.

A third patient, a 24 year old male with generalized Hodgkin's disease who presented diffuse enlargement of the liver on clinical examination and whose scan (Fig. 3*A*) revealed hepatomegalia with mild infiltration of Hodgkin's disease throughout the liver, was treated by a course of intravenous prednisone and Velban. Despite the symptomatic improvement, with the control of fever and pruritus, plus a decrease in the serum alkaline phosphatase from 12.4 S.J.R.* units to 8.0 S.J.R. units, a repeat scan did not reveal any significant change in the hepatic topography (Fig. 3*B*). These data suggest that the hepatic gammascanning procedure is not sufficiently sensitive to distinguish that degree of Hodgkin's neoplasia which will produce symptoms from that which will not.

Nodular Involvement of the Liver by Hodgkin's Disease. A minority of patients will present nodular involvement of the liver by Hodgkin's disease. The nodules can be massive, with encroachment upon contiguous organs to produce pressure symptoms or to create a sensation of distention. One such patient was a 22 year old female with Stage III Hodgkin's disease, whose hepatic photoscan disclosed hepatomegalia with nodular involvement of the left lobe impinging upon the right lobe (Fig. 4*A*). She received external irradiation, 2,400 rads in 15 days with the orthovoltage generator, which produced marked relief of the pain and a significant reduction in the size of the liver. However, she succumbed from generalized Hodgkin's disease about 1 month later, and necropsy revealed a large region of nodular Hodgkin's granuloma at the site demonstrated by the defect on the scan. The nodular region showed marked fibrosis and necrosis, presumed to be the result of the radiation therapy, surrounded by normal hepatic tissue (Fig. 4*B*).

Another patient was a 46 year old female with Stage II Hodgkin's disease. Figure 5 is the hepatic photoscan showing the hepatomegalia and nodular Hodgkin's disease. She was treated by intravenous Velban (vinblastine), and prednisone. Although the size of the liver remained constant, the nodular defect within the liver lessened markedly to palpation after the chemo-

* Shinowara-Jones Reinhart; normal, 4–8 units/100 cc.

therapy. The patient remains symptom free and is being maintained on chlorambucil.

LYMPHOSARCOMA

Hepatic scintillation scanning is of clinical value in determining the presence of liver involvement in patients with lymphosarcoma. Hepatic photoscans were done in 13 patients with either Stage II (regional) or Stage III (generalized) lymphosarcoma (Table II). Two of these patients had reticulum cell sarcoma.

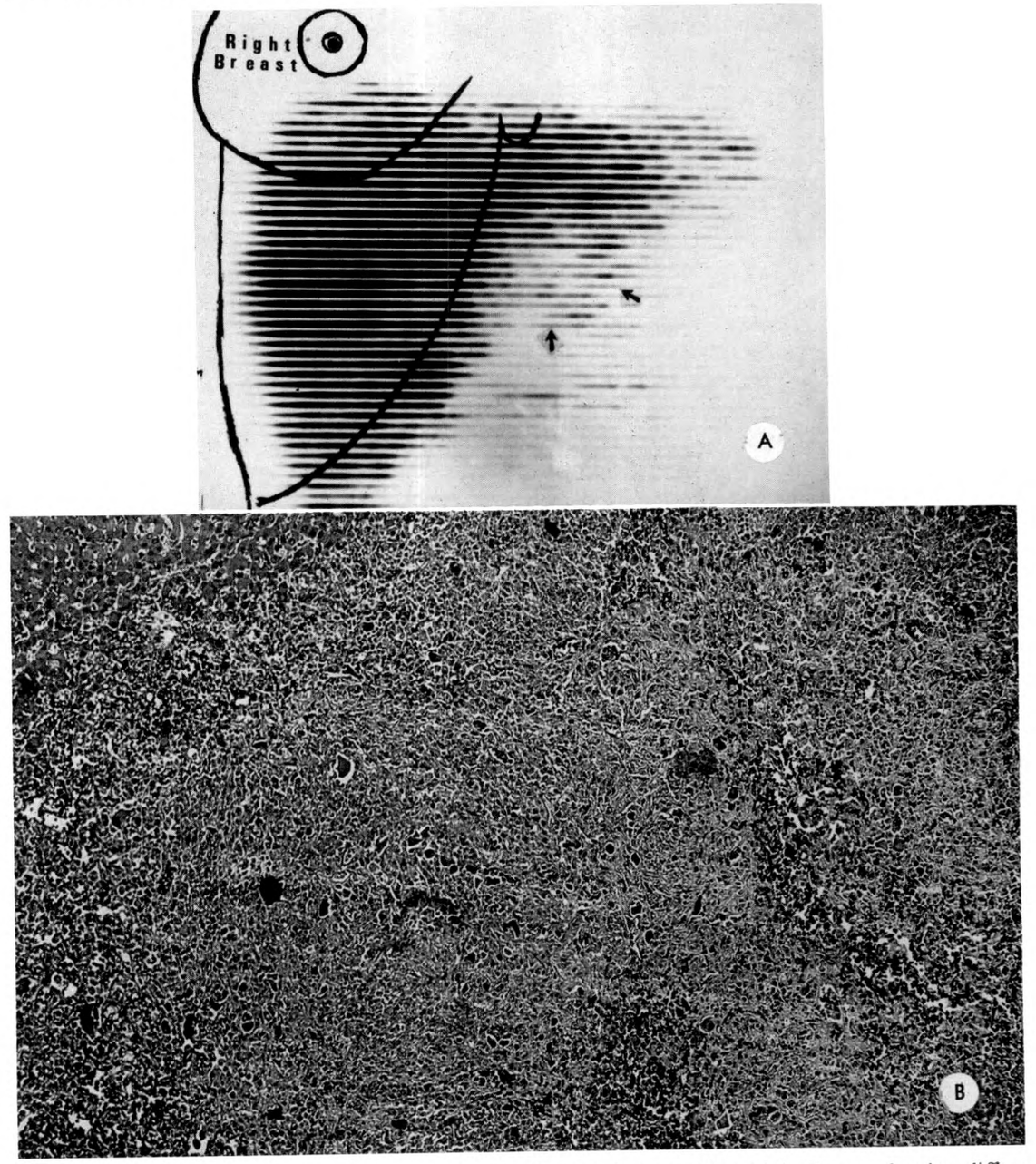


FIG. 4. (*A*) Hepatic photoscan in a 22 year old female with Stage III Hodgkin's disease, showing diffuse nodular enlargement. Radiation therapy, consisting of 2,400 rads in 15 days to her epigastrium, gave relief of pain and caused reduction in the size of the hepatic mass. (*B*) Necropsy photomicrograph of the liver shows a large region of Hodgkin's granuloma with considerable fibrosis and necrosis. Normal liver tissue is seen in the right upper corner.

One patient with lymphosarcoma, a 53 year old female, presented an enlarged liver with mesenteric and para-aortic lymph node masses. The diagnosis was established by biopsy at laparotomy. Her initial photoscan (Fig. 6*A*) revealed hepatic enlargement with irregular patchy infiltration involving the upper portion of the left lobe and extending to the right lobe of the liver. Following radiation therapy, consisting of 3,000 rads tumor dose given in 3 weeks to the abdomen, the liver was no longer palpable and the mesenteric and para-aortic masses had diminished in size. A second scan (Fig. 6*B*) 6 months later showed a few irregularities consistent with lymphosarcoma. Clinically, the patient has been asymptomatic and has been maintained on chlorambucil given intermittently. A third liver scan in 5 months showed no significant change (Fig. 6*C*).

Seven patients were clinically suspected of having small cell lymphosarcomatous hepatic involvement because of a palpably enlarged liver and abnormal liver function tests. Their hepatic photoscans were compatible with the clinical diagnosis. In one of these patients, who came to necropsy, histologic examination showed diffuse

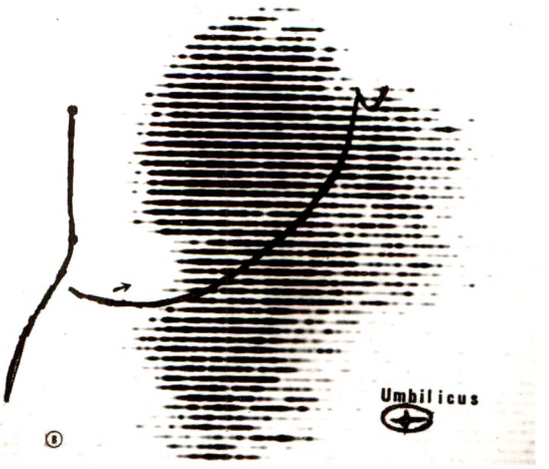
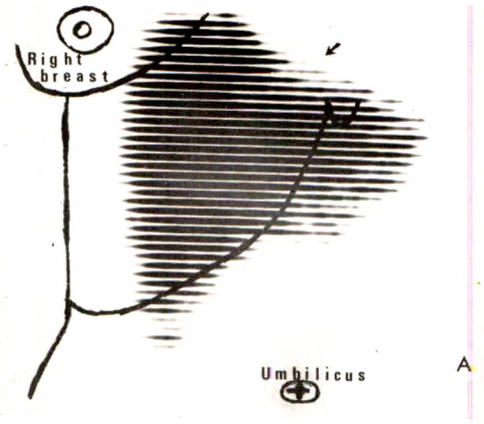


Fig. 5. Hepatic photoscan in a 46 year old female with Stage II Hodgkin's disease, showing diffuse nodular enlargement, controlled by intravenous prednisone and Velban.



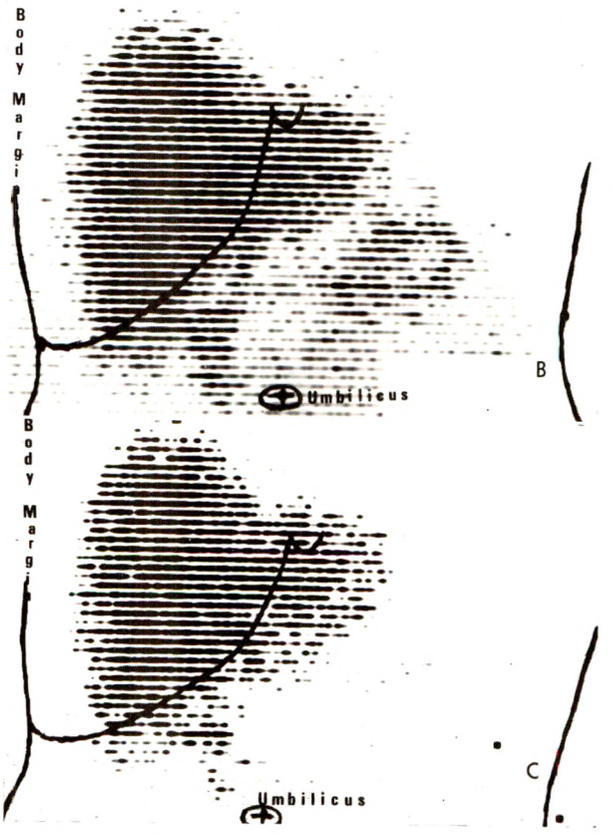


Fig. 6. (*A*) Hepatic photoscan in a 53 year old female with Stage II lymphosarcoma, showing hepatic enlargement and patchy lymphosarcomatous infiltration involving the upper left and right lobes. External irradiation, 3,000 rads, was given to the liver and mesenteric and para-aortic masses, with nearly complete resolution of all palpable masses. (*B*) Repeat scan 6 months later showed a few irregularities consistent with lymphomatous infiltration. (*C*) Hepatic scan in 5 months showed no significant change. The patient has been maintained on chlorambucil and is symptom free.

TABLE II

LIVER SCANS IN 13 PATIENTS WITH LYMPHOSARCOMA

Patient No.	Age (yr.)	Sex	Scan pattern		Necropsy	Comment
			Initial	Repeat		
1	53	F	Diffuse enlargement, patchy infiltration April, 1964	Smaller, fewer irregularities after irradiation, October, 1964; no change, March, 1966		Response to irradiation confirmed by repeat scan. No further activity; maintained on chemotherapy
2	46	M	Diffuse, patchy infiltration, nodules		None	
3	76	M	Diffuse, patchy infiltration		None	
4	58	F	Diffuse, patchy infiltration		Diffuse infiltration	
5	56	F	Diffuse, patchy infiltration		Diffuse infiltration	
6	69	F	Diffuse, patchy infiltration			Response to irradiation and chemotherapy
7	40	M	Normal		None	Extrahepatic lymphosarcoma
8	53	M	Patchy infiltration, suggested nodular involvement			Alive; response to roentgen therapy; maintained on chemotherapy
9	46	M	Normal			No evidence of liver involvement; Stage III; on chemotherapy
10	55	M	Normal			Stage II; no liver involvement
11	54	M	Normal			Alive; free of disease after irradiation to abdomen
12	4	M	Diffuse enlargement, patchy infiltration		Diffuse infiltration	Died 2 months after irradiation to abdomen
13	30	M	Small liver October, 1965	Scan January, 1966 after intravenous Cytoxan; no change		Disease controlled with chemotherapy

parenchymal infiltration, previously diagnosed by the photoscan (Fig. 7, *A* and *B*). Another patient presented a palpable nodular mass in the right subcostal region extending 3 fingerbreadths beneath the 12th rib. On the basis of the scan (Fig. 8), which revealed a relatively small liver with an irregular border of the right lobe, a diagnosis was made of extrahepatic lymphosarcoma and appropriate irradiation was administered. The patient expired several months after radiation therapy. No necropsy was performed.

Figure 9 is the hepatic photoscan of a 4 year old boy with generalized reticulum cell sarcoma, and demonstrates diffuse hepatic lymphomatous involvement with hepatomegalia and extensive mesenteric and retroperitoneal lymphomatous involvement. Necropsy confirmed the diagnosis made by the photoscan.

Diagnosis of Nonlymphomatous Involvement in a Patient with Reticulum Cell Sarcoma. Figure 10 is the hepatic photoscan of a 30 year old obese male with Stage III reticulum cell sarcoma. His liver function tests were within normal limits. The scan revealed a liver of small size. In view of the fact that the diagnosis, based on this scan, was of either cirrhosis or some other parenchymatous hepatic disorder unrelated to the lymphomatous process, it was de-

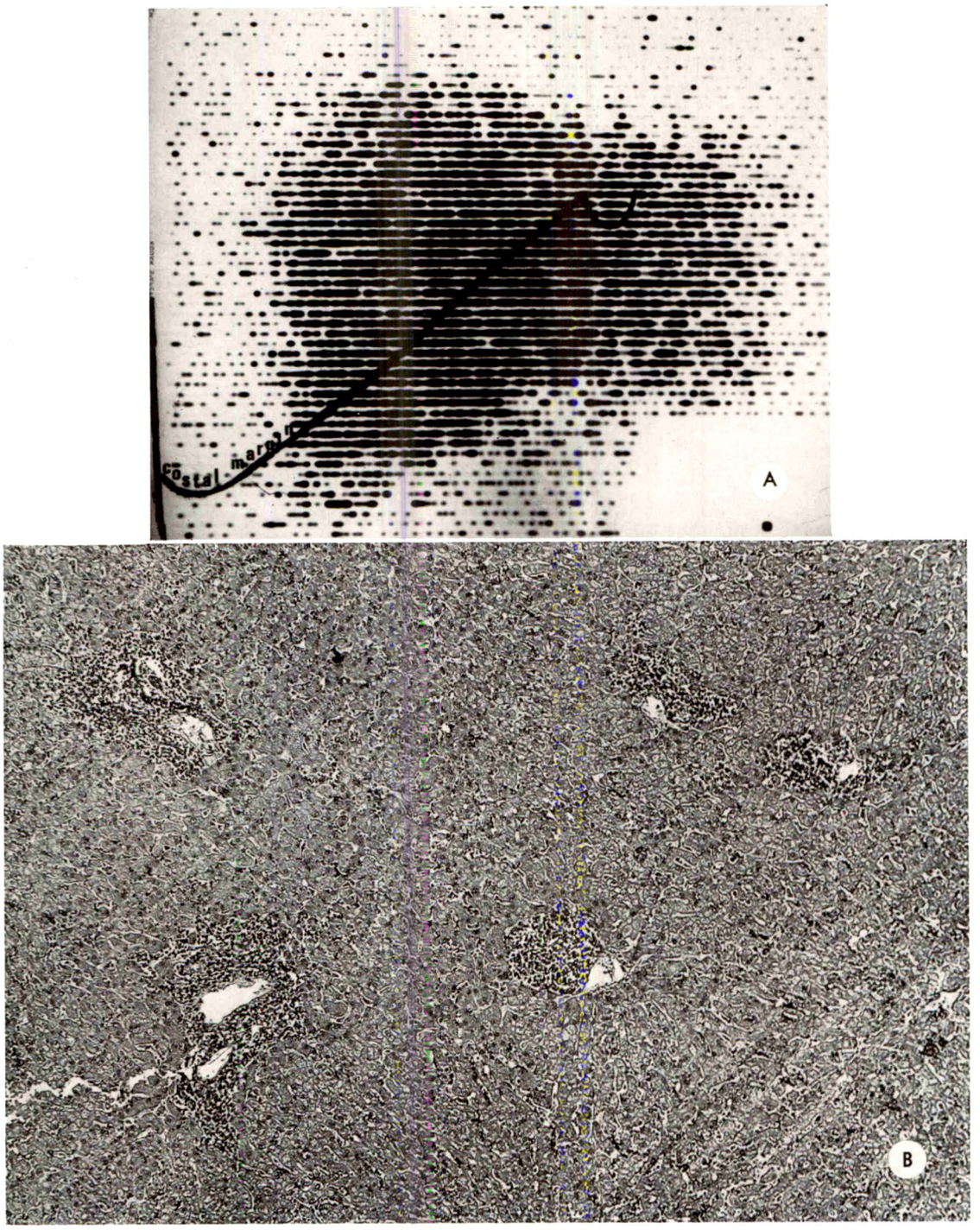


Fig. 7. (*A*) Hepatic photoscan in a 58 year old female, diagnosed clinically as suffering from small cell lymphosarcomatous involvement of the liver, shows a diffuse erratic pickup compatible with the clinical diagnosis. (*B*) Necropsy photomicrograph of the liver reveals periportal and central infiltration by small lymphocytic cells, confirming the diagnosis made by scan.

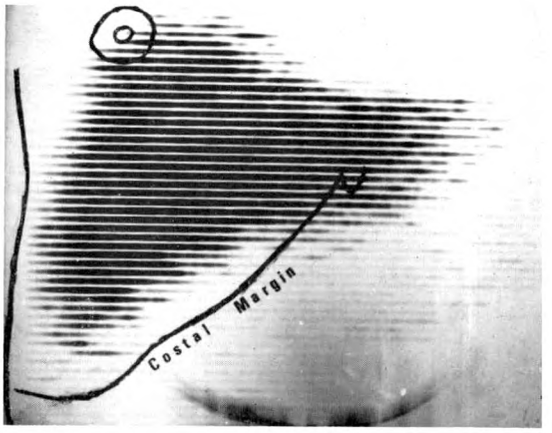


Fig. 8. Hepatic scan in a 40 year old male which revealed a relatively small liver and an irregular border surrounding the right lobe; diagnosed as extrahepatic lymphosarcoma and appropriate treatment given.

cided to treat this patient with very small doses of cancer chemotherapeutic agents. This was done in an effort to protect the liver against the noxious effects of the chemotherapeutic agents. The small doses of Cytoxan produced marked clinical improvement and he continues to be well. A repeat scan revealed no evidence of change in the architecture of the liver.

DISCUSSION

Hepatic gammascanning is a useful procedure which serves to aid the clinician in the treatment of patients with malignant lymphoma. The greatest difficulty with this procedure lies in the fact that much of the lymphomatous involvement of the liver consists of diffuse parenchymatous infiltration, and a similar picture is produced by such nonlymphomatous disorders as hepatitis, fatty degeneration, early stages of cirrhosis, etc. Therefore, one cannot make an absolute diagnosis of diffuse parenchymatous infiltration by malignant lymphoma; a correlation between the hepatic function tests and the scintiscan can be helpful in the differential diagnosis. As a rule, the hepatic function tests as observed in hepatitis or in the posthepatitis syndrome are less favorable than those observed in the malignant lymphomas. The serum transaminase level may be very high in hepatitis in contrast to either a normal or slightly elevated level in patients with malignant lymphoma. The alkaline phosphatase level in both instances will depend, not only upon the degree of parenchymatous damage, but also upon the

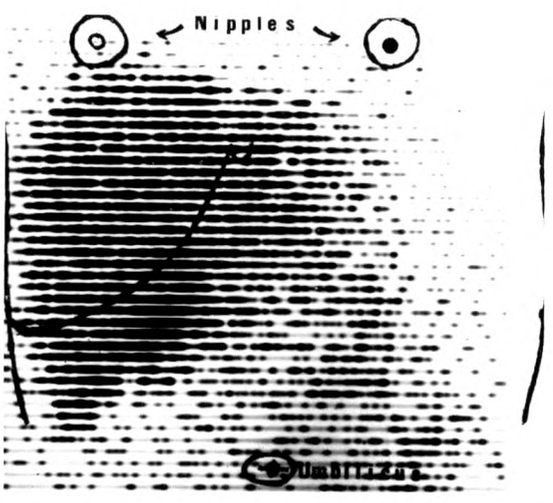


Fig. 9. Hepatic photoscan in a 4 year old boy with generalized reticulum cell sarcoma demonstrates hepatomegalia plus extensive mesenteric and retroperitoneal lymphomatous involvement. Necropsy confirmed the diagnosis made by photoscan.

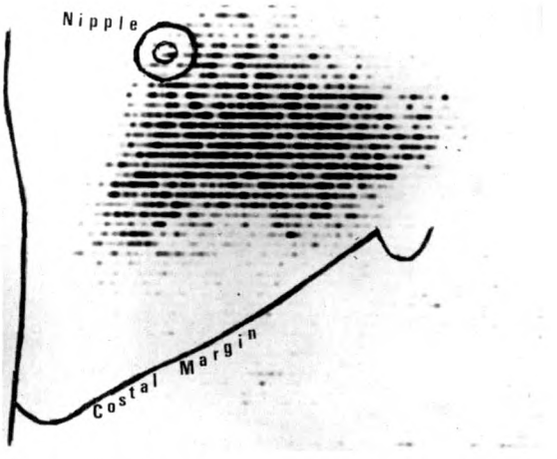


Fig. 10. Hepatic photoscan in a 30 year old male with Stage III reticulum cell sarcoma showing a liver of small size, diagnosed as either cirrhosis or other parenchymatous hepatic disorder unrelated to the lymphomatous process. Smaller than normal doses of Cytoxan were given with marked clinical improvement.

amount of obstruction present. As a general rule, the thymol turbidity and cephalin flocculation tests will be normal in patients with malignant lymphoma, whereas an abnormal value is observed in other liver disorders. Accordingly, a nicety of judgment is necessary in the differential diagnosis between idiopathic parenchymatous disease of the liver and diffuse infiltration by malignant lymphoma.

On the basis of clinical application of the above observations, a number of patients, not only with known malignant lymphoma but those suspected of having hepatic lymphomatous involvement, were treated by cancer chemotherapeutic agents and/or external radiation therapy. Improvement occurred in a few of these patients. However, those patients in whom the lymphomatous process had become too extensive expired from their disease. In 5 of these patients, the diagnoses made on the basis of the scintiscan were confirmed by the necropsy findings.

The significance of these observations is corroborated by the fact that in 3 patients with Hodgkin's disease who expired, necropsy findings confirmed the diagnosis of diffuse and/or nodular infiltration of the liver by Hodgkin's disease in 2 patients. In 6 patients with lymphosarcoma who expired, necropsy revealed 3 patients to have diffuse infiltration by lymphosarcoma as diagnosed by scan.

Nodular involvement of the liver by malignant lymphoma is more readily diagnosed by hepatic gammascan, and the scan may function as an aid in determining the portals for giving external irradiation, should this be indicated. Moreover, if a questionable diagnosis exists, and there is no contraindication to an aspiration biopsy, the scan may help to pinpoint the target for the aspiration biopsy.

Hepatic gammascanning can be useful as a means for following the course of treatment in a patient with a diagnosed malignant lymphoma of the liver. The scan will demonstrate any shrinkage of the liver as well as any regression of the neoplastic nodules; it will also show the reverse conditions. In several of our patients, a clinical symptomatic response occurred following the administration of cancer chemotherapy and/or steroids, without evidence of change in the hepatic scan. In this instance, apparently the symptomatic response was the result of a highly sensitive mechanism not reflected in the hepatic gammascan.

There are times when hepatic gammascanning may serve to distinguish between a malignant lymphoma and some other disorder of the liver. Thus, one of our patients, a very obese male with a comparatively small liver diagnosed as being postnecrotic cirrhosis, was given much smaller doses of cancer chemotherapeutic agents than are ordinarily administered, in an effort to prevent further traumatization of the liver. The therapy was well tolerated and the patient showed improvement.

CONCLUSIONS

Scintillation scanning of the liver by I^{131} rose bengal is a useful adjunctive procedure for determining the presence or absence of hepatic involvement by malignant lymphoma.

The most common pattern of hepatic involvement, in a limited review of patients with Stage II or Stage III lymphomatous disease, appears to be a diffuse, patchy infiltration.

Serial scans are useful for following the resolution and control of lymphomatous hepatic involvement.

There does not appear to be any specific correlation between the liver scans and liver function tests.

Hepatic scintiscans may aid in detecting the presence of nonmalignant parenchymatous liver disease in patients with lymphomas.

Further study is planned to include liver biopsies in association with the clinical interpretation of these patients.

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VOL. 99, NO. 4

PLEURAL MESOTHELIOMAS*

CLINICAL EXPERIENCES WITH THIRTY-SEVEN PATIENTS

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PLEURAL mesotheliomas are rare tumors, often difficult to diagnose and discouraging to treat. Individual experience with them is still limited, although there is some indication that the incidence of the disease may be increasing.[1–3,5,6,11,13,15–19,21] This review of Memorial and James Ewing Hospital patients with pleural mesothelioma was undertaken to clarify the clinical presentation and natural history of these tumors, and to evaluate the various forms of treatment which have been used.

MATERIAL

The clinical records of all Memorial and James Ewing Hospital patients with the diagnosis of mesothelioma, pleural sarcoma, pleural cancer, or other pleural tumor during the years 1937 to 1965 were reviewed. Histologic material from all clinically acceptable cases was critically re-examined. Patients were excluded from the study if there was any doubt clinically or pathologically about the site of origin of their tumor, or if they had another cancer in addition to mesothelioma. From over 200 possible cases, 37 completely satisfied these criteria and were selected for this review.

PATHOLOGY

The tumors were classified into the following 4 categories according to their gross and microscopic characteristics.

Pleural Mesotheliomas	*No. of Patients*	
Benign Fibrous Mesothelioma		
Cellular	2	
Sclerosing	4	
		6
Malignant Mesothelioma		
Epithelial	16	
Fibrosarcomatous	15	
		31
Total		37

BENIGN FIBROUS MESOTHELIOMA

All 6 patients with benign mesotheliomas had tumors presenting as solitary, circumscribed or encapsulated large masses. The 2 cellular fibrous mesotheliomas measured 12 cm. and 18 cm. respectively; the larger one was adherent to pericardium. The 4 sclerosing tumors ranged from 5 cm. to 14 cm. in diameter; 2 were attached only by pedicle to the pleura, 1 to visceral and 1 to parietal pleura, and 2 were located within interlobar fissures.

Both cellular fibrous mesotheliomas were lobulated, reddish, firm though not hard, and centrally cystic (Fig. 1). Histologically,



FIG. 1. Benign cellular fibrous mesothelioma. This huge, lobulated, encapsulated tumor was successfully removed and the patient is living and well without recurrence.

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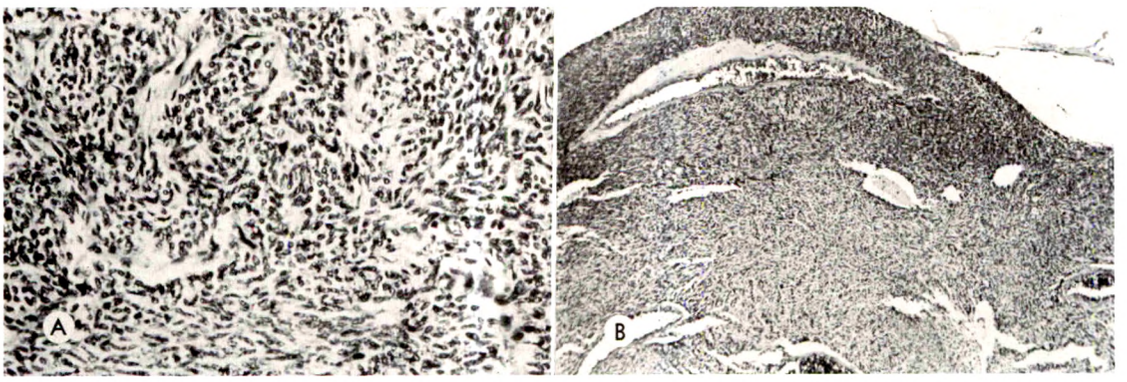


Fig. 2. (*A* and *B*) Benign cellular fibrous mesothelioma. Nuclei are numerous and ovoid, but bland and very regular, and mitoses are rare. The tumor is well circumscribed and very vascular. This is the same tumor illustrated in Figure 1. (H & E, *A:* 140x; *B:* 35x.)

well preserved areas were very cellular, composed of rather uniform, small, ovoid cells with regular nuclei and scanty cytoplasm. A delicate connective tissue framework carried numerous thin walled, narrow capillaries between the small nests and rows of cells (Fig. 2, *A* and *B*). Hemorrhage was common, as well as areas of necrosis and liquefaction. Mitoses were rare. The uniformity of cell architecture in these 2 cases distinguished them from low grade fibrosarcomas.

The 4 sclerosing fibrous mesotheliomas were gray or white on cross section, with areas of hemorrhage. They were variable in consistency (Fig. 3). Histologically, they were characterized by abundant, dense collagenous stroma and thin spindle cells with elongated, narrow, dark staining nuclei. These tumors were much less cellular than the preceding type. Mitoses were rare, if present at all (Fig. 4, *A* and *B*).

MALIGNANT MESOTHELIOMA

Epithelial Mesothelioma. There was some variation in the gross appearance of these tumors, in part attributable to the stage of disease. Generally, they appeared as poorly demarcated areas of pleural thickening. The earliest lesions were multiple, small, white or gray granules, nodules, or flakes appearing on normal or slightly opaque visceral or parietal pleura. With advancing disease the pleural surfaces became progressively thicker and more granular, nodular, or lobulated. Thickened areas of parietal and visceral pleura became adherent, and fused, leaving loculated cavities containing straw-colored or bloody fluid. Areas of hemorrhage, cystic degeneration and necrosis were common in larger tumor masses, giving a variegated appearance to otherwise gray or tan tissue. Texture ranged from firm or rubbery to soft and friable.

The tumors involved mainly the lower hemithorax, particularly the posterior and medial costophrenic angles. With increasing size, they displaced the lung upward, compressing and constricting it by envelopment. Superficial invasion of pulmonary parenchyma was very common, and often

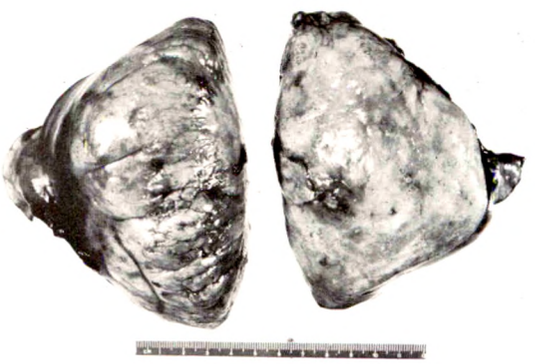


Fig. 3. Sclerosing fibrous mesothelioma. This encapsulated, firm, grayish-white tumor has the gross appearance of a benign fibroma.

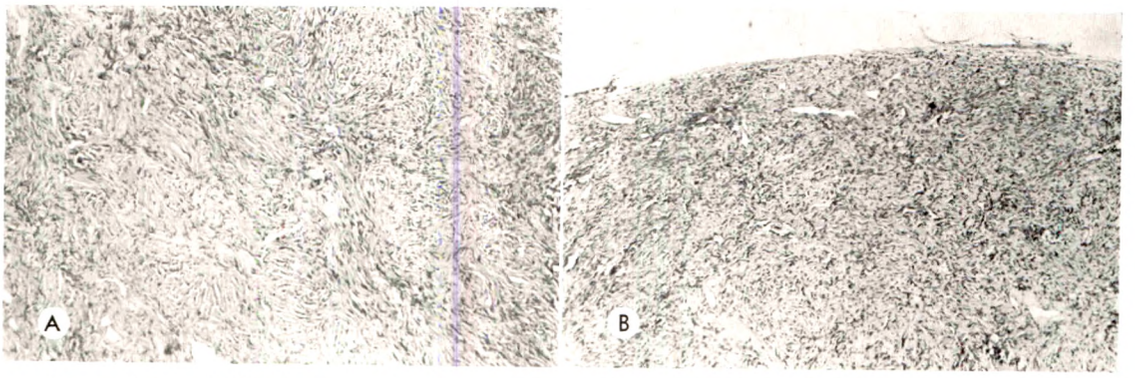


Fig. 4. (*A* and *B*) Benign sclerosing fibrous mesothelioma. Note the dense collagenous stroma and relatively infrequent, thin nuclei. The tumor margin is sharply defined. (H & E, 35x.)

there was a rather deep extension into the lung and the mediastinum (Fig. 5). Discrete metastases, particularly to mediastinal lymph nodes, were also common late in the disease.

Other sites of metastases were opposite lung, supraclavicular lymph nodes, subcutaneous tissue particularly of chest wall, abdominal lymph nodes, bone and abdominal viscera. The contralateral pleura was commonly involved, and at times also the peritoneum; this may be an indication of multicentric origin rather than metastases (Table 1).

The histology of these tumors was variable, but 3 predominant patterns were observed, always reflecting some form of proliferation of surface mesothelial cells: delicate papillary fronds supported by stalks of connective tissue; loosely aggregated medullary masses, composed of tumor cells only; and proliferating mesothelium in nests or linear strands of cells, usually with a marked desmoplastic reaction. Sometimes gland-like structures, mimicking bronchiolar lung cancer or other adenocarcinomas, were present (Fig. 6 through 10). To establish the correct diagnosis, it was helpful to demonstrate the continuity of neoplastic mesothelial cells



Fig. 5. Epithelial mesothelioma, at autopsy, growing along pleural surfaces and compressing the lungs. Note that the tumor mass is located predominantly in the lower half of the thorax and that invasion into the lung has occurred. This tumor was unusual in the bilateral presentation. Paratracheal lymph node metastases are present.

Table I

SITES OF METASTASES FROM EPITHELIAL MESOTHELIOMAS

Site	Clinical	Autopsy*
Opposite pleura and/or lung	2	4
Mediastinal lymph nodes	—	4
Peritoneum	1	2
Supraclavicular lymph nodes	4	—
Pericardium	—	3
Subcutaneous nodules	5	—
Bone	1	—
Pancreas	—	1
Abdominal lymph nodes	—	1

* Four patients.

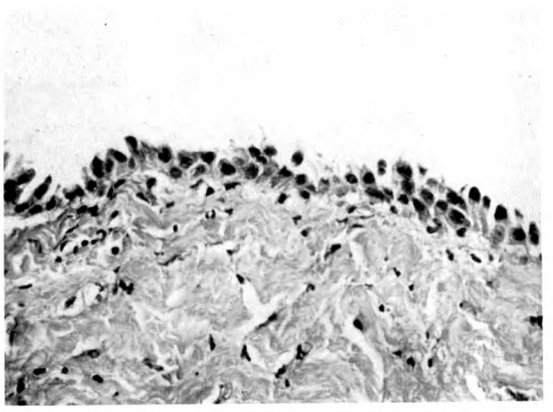


Fig. 6. Malignant epithelial mesothelioma. The tumor in this area is several cell layers thick, but still retained on the surface. This is interpreted as a very early stage of development. Note the dense desmoplasia of underlying stroma. (H & E, 350x.)

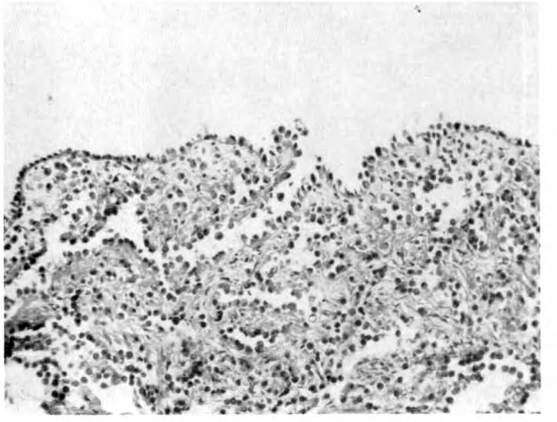


Fig. 8. Malignant epithelial mesothelioma. Tumor cells extend from the surface, where they are in continuity with adjacent non-neoplastic mesothelial cells, into sinusoids and channels within the stroma. (H & E, 140x.)

with adjacent mesothelium *in situ*. The single layered mesothelial cells in adjacent areas, and sometimes more distantly, characteristically became very tall and peg or club-shaped, somewhat resembling a "picket fence" (Fig. 11, *A* and *B*). In the papillary or medullary areas, the neoplastic mesothelial cells tended to be fairly large with abundant eosinophilic cytoplasm, large vesicular nuclei, prominent nuclear membrane, which was often wrinkled, and prominent nucleoli. Where the cells lay in strands or nests within a dense fibrous stroma, they were smaller and darker staining. Spindle metaplasia of mesothelial cells was sometimes noted, but no purely spindle cell tumors were classified in this category. Within the tumor vacuolated mesothelial cells were frequent, and within the stroma myxoid or mucinoid areas were sometimes observed (Fig. 12). Unlike mucin producing adenocarcinomas, however, no mucicarminophilic material was demonstrable either in tumor cells or in stroma.[4]

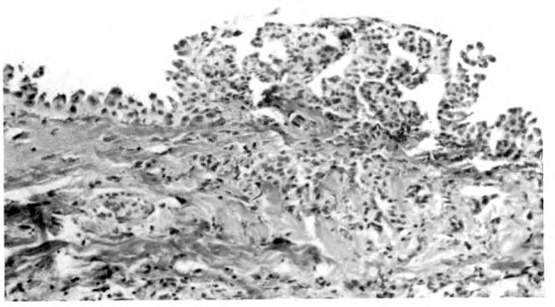


Fig. 7. Malignant epithelial mesothelioma. Proliferating mesothelial tumor cells here form small papillary projections as well as infiltrating nests and small solid masses of tumor cells. (H & E, 140x.)

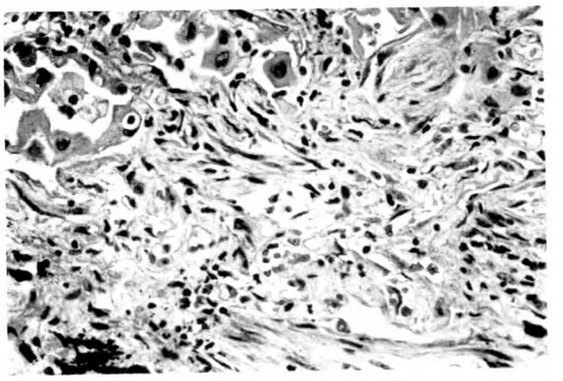


Fig. 9. Nests of epithelial mesothelioma mimicking adenocarcinoma and lying within a cellular fibrous stroma which may be partly formed by metaplasia of the mesothelial cells. This patient had preoperative irradiation which may account for some of this pattern. (H & E, 350x.)



Fig. 10. Epithelial mesothelioma with desmoplastic reaction. At this relatively late stage the pleural space has been largely obliterated. Parietal and visceral pleurae here are fused except for a few clefts and sinusoidal channels lined by malignant mesothelial cells. (H & E, 35x.)

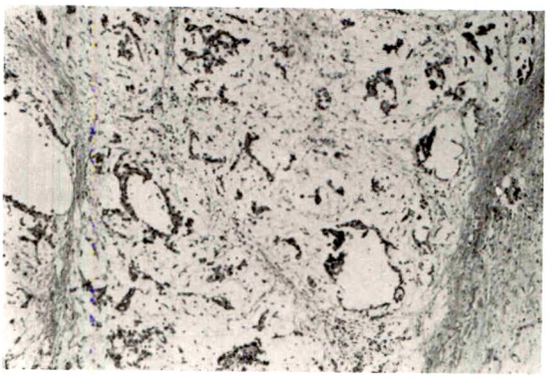


Fig. 12. Epithelial mesothelioma with myxoid stroma resembling some mucus-secreting adenocarcinomas. This tumor contained no mucicarminophilic material. (H & E, 35x.)

Fibrosarcomatous Mesothelioma. These tumors were characterized by their gross and histologic similarity to fibrosarcomas originating elsewhere in the body. They were already bulky when the patients were first seen by us. Unlike the epithelial mesotheliomas, they tended to be fairly discrete or circumscribed, though not truly encapsulated. On cut surface, the tumor masses varied in appearance and texture. Some were white or gray and densely fibrous with interlacing trabeculae; others were brown or fleshy, soft and friable. Focal hemorrhage, necrosis, and cystic degeneration resulted in reddish or yellowish discoloration and localized softening or liquefaction (Fig. 13).

The histologic pattern was also that of fibrosarcomas generally (Fig. 14 and 15). There were orderly, interwoven bundles of plump spindle cells with frequent mitoses and, in other areas, looser, disarranged aggregates of spindle or stellate cells. Multinucleated tumor giant cells were common. Typically, the tumors were richly cellular, but contained variable amounts of collagen. The surface layer of mesothelial cells was sometimes caught between tumor nodules and gave an impression of an epithelial component but they were not considered part of the neoplasm proper. Tumor extension into adjacent lung or other tissue occurred to varying degree

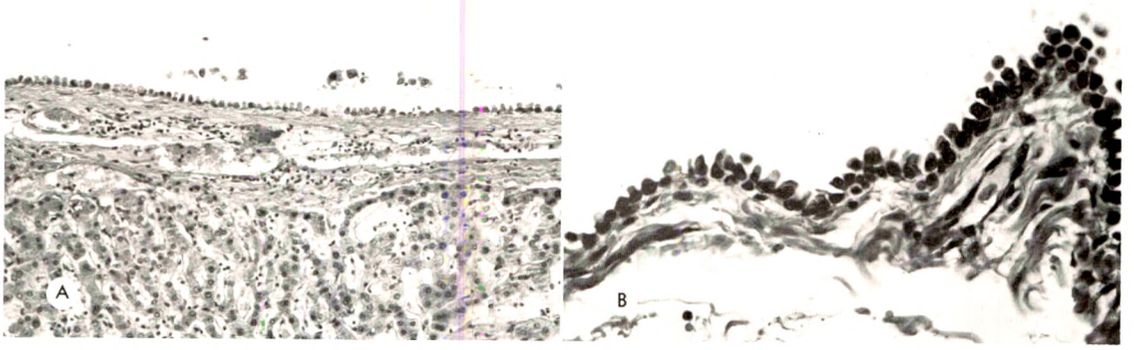


Fig. 11. (*A* and *B*) Mesothelium on the surface of the (*A*) liver and (*B*) mesentery away from the site of an epithelial pleural mesothelioma. Note the "picket fence" prominence of these mesothelial cells. Is this an early neoplastic change suggesting multicentric origin? (H & E, *A:* 140x; *B:* 350x.)

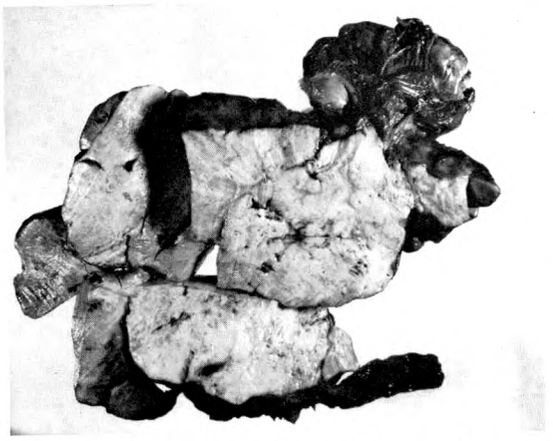


FIG. 13. Fibrosarcomatous mesothelioma. This tumor resembles fibrosarcomas as they occur elsewhere in the body. There is infiltration into adjacent lung tissue despite apparent circumscription.

(Fig. 13). Distant metastases to the opposite lung and pleura, long bones, ribs, muscle, brain, spinal cord and subcutaneous tissue were observed (Table II).

GENERAL CLINICAL DATA

Most of the patients were in their 6th and 7th decades. The ages of the patients with the benign tumors ranged from 31 to 72 years, with a median of 53 years. The ages of the patients with malignant tumors ranged from 13 to 70 years, with a median of 54 years. It is of interest that 3 of the patients with fibrosarcomatous mesotheliomas were less than 20 years old, 13, 16 and 18 years of age respectively, and 7 were less than 35 years old. The youngest patient with an epithelial mesothelioma was 30, and all of the others were more than 45 years old.

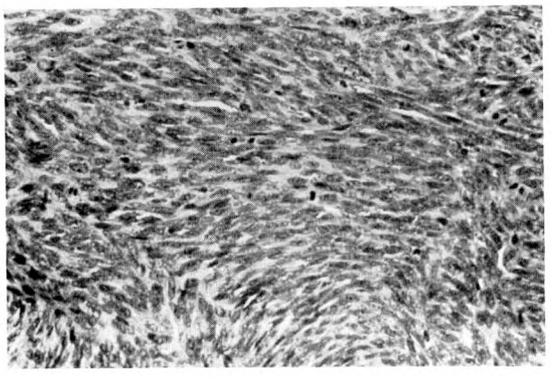


FIG. 14. Malignant fibrosarcomatous mesothelioma. Nuclei are crowded, plump, and vesicular, and many are in mitosis. This pattern is seen in many fibrosarcomas, regardless of site of origin. (H & E, 140X.)

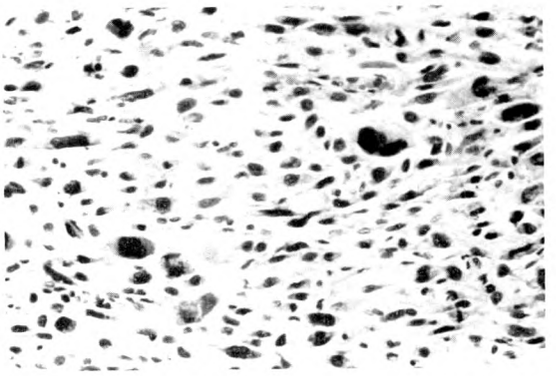


FIG. 15. Malignant fibrosarcomatous mesothelioma. This spindle and giant cell pattern may be found in many soft tissue sarcomas. (H & E, 140X.)

There were 3 men and 3 women with benign tumors, and 21 men and 10 women with malignant tumors. Thirty-six of the 37 patients were white. The 1 Negro was male and he had an epithelial mesothelioma. Of the 31 malignant tumors, 20 were right sided and 11 left sided; of the 6 benign tumors, 4 were right sided and 2 were left sided.

One patient, who had an epithelial mesothelioma, had worked in an asbestos factory for 15 years. Three others had

TABLE II

SITES OF METASTASES FROM FIBROSARCOMATOUS MESOTHELIOMAS*

Site	Clinical	Autopsy†
Brain	2	—
Spinal cord	3	—
Branchial plexus	1	—
Bone	2	—
Subcutaneous nodules	3	—
Opposite lung and pleura	1	—
Muscle	1	—

* Distant metastases occurred in 8 patients; the 3 autopsied patients and 4 others had disease confined to the hemithorax with local extension to mediastinum and chest wall.

† Three patients.

been employed in the construction industry where exposure to asbestos might have occurred. None of the remaining patients was known to have been exposed to asbestos. Interestingly, asbestos bodies were found in histologic sections of the lung from only 2 patients, both at autopsy and neither had been thought to have had exposure to asbestos. One had an epithelial mesothelioma, and the other a fibrosarcomatous mesothelioma.*

The smoking habits were known for 18 of the 31 patients with malignant tumors, and 11 were considered heavy smokers. Only 1 of the 6 patients with benign tumors was a heavy smoker.

SYMPTOMS

Benign Tumors. All the patients with benign tumors were essentially asymptomatic when first seen. Their tumors were discovered incidentally on chest roentgenograms. The 2 patients with cellular fibrous mesotheliomas did have mild chest discomfort, but in both instances the pain was of several years' duration and caused little concern. Neither sought medical aid for this symptom.

Dyspnea, cough, weight loss, anorexia, and fatigue were subsequently mentioned by 1 or more patients, but were mild and nonprogressive. Two patients had arthritis, 1 severe, and arthritic manifestations subsided in this latter patient when the tumor was removed.

Malignant Tumors. The patients with epithelial and fibrosarcomatous mesotheliomas had similar symptoms and can be discussed as a single group.

Twenty-two of the 31 patients had chest pain as their initial complaint, and 28 had it at some time during the course of their illness. The pain varied from a dull twinge to a severe ache and was located on the side of the tumor. Its relationship to breathing was variable.

Two patients had dyspnea alone as their initial symptom; 6 others had dyspnea coexistent with chest pain as an initial symptom. Twenty-three of the 31 patients had dyspnea as a significant complaint at some time during their illness.

Cough was the initial symptom in 4 of the 31 patients, and 6 others developed a significant cough during the course of their illness. Most were either nonproductive or productive of only small amounts of whitish mucus. Two patients had hemoptysis.

In 3 patients the initial symptomatology could not be elucidated.

Fatigue, anorexia, malaise, nervousness, dysphagia, tightness in the chest, backache, weight loss, lethargy, palpitations, night sweats, chills, frequent colds, laryngitis, "allergy," asthma, sinusitis and hoarseness were all reported during the course of their illness by one or more patients.

Two patients presenting with chest pain had spontaneous pneumothorax. The first, a 63 year old man, was treated by pleurectomy for persistent pneumothorax with effusion and an epithelial mesothelioma was discovered in the removed pleura. The second, a 31 year old female, had a hydropneumothorax when seen initially. She was treated only by repeated thoracenteses; at postmortem examination, a fibrosarcomatous mesothelioma was discovered. Another patient, an 18 year old girl, had a pneumothorax at 14 years of age and pleurectomy was done because of failure of re-expansion. No evidence of mesothelioma was found in histologic sections of the removed pleura on subsequent review. Four years later she developed chest pain on the opposite side and a fibrosarcomatous mesothelioma was discovered and removed at thoracotomy.

PHYSICAL FINDINGS

Benign Tumors. Five of the 6 patients with benign tumors had normal physical examinations of the chest. The remaining patient had dullness to percussion and decreased breath sounds in the area of a bulky tumor.

Malignant Tumors. The physical findings

* We are indebted to Dr. L. R. Stern, St. Mary's Hospital, Hoboken, N. J., for an opportunity to review the autopsy findings in this case.

in patients with malignant tumors varied with the stage of the disease. When first seen, most of the patients had signs of fluid in the involved hemithorax with flatness to percussion and decreased breath sounds. As the tumors increased in size, the signs of local chest involvement became more marked—obvious enlargement of the affected hemithorax, bulging of the intercostal spaces, and deviation of the trachea to the opposite side. The local tumor growth also caused depression of the diaphragm and displacement of the liver or the spleen, giving an impression of hepatomegaly or splenomegaly. There was no parenchymal invasion of either liver or spleen in any of our cases.

Congestion and edema developed late in the course of the disease in a few patients, involving the upper limbs and head and neck, or the lower limbs, or both, sometimes with ascites. This was usually attributable to tumor compression of the superior or inferior vena cava, or both. A less common mechanism of ascites formation in patients with epithelial mesotheliomas was probably by direct tumor growth as "implants" on the serosal surface, and in 1 such case cancer cells were demonstrable in ascitic fluid.

Supraclavicular and axillary lymph node enlargement, subcutaneous nodules, and bone tenderness (all secondary to metastases) were present in several patients later in their illness.

DIAGNOSTIC STUDIES

CHEST ROENTGENOGRAMS

Benign Tumors. The benign tumors were all discovered as a mass on chest roentgenograms. None of these patients had pleural effusion (Fig. 16*A*).

Malignant Tumors. Pleural effusion was discovered initially in all but 1 of the patients with epithelial mesothelioma (Fig. 17, *A* and *B*). In that single exception, "pleural nodules" were described, but unfortunately the roentgenograms were no longer available for our review. None of the other patients had demonstrable masses, even after withdrawal of the chest fluid (Fig. 18, *A* and *B*).

Pleural effusion was discovered initially in 8 of the patients with fibrosarcomatous mesotheliomas; the other 7 were found to have intrathoracic masses. Interestingly, all 3 of the patients who were less than 20 years old presented with a mass. Four of the 7 patients presenting initially with an intrathoracic mass eventually also developed effusion. Thus, 12 of 15 patients with

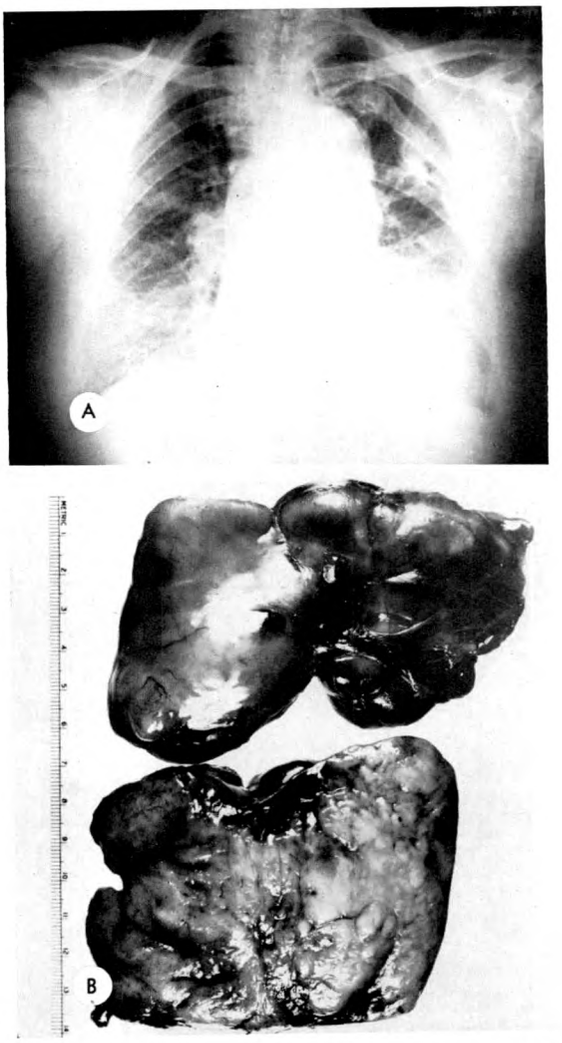


FIG. 16. (*A*) Chest roentgenogram of 63 year old woman with cellular fibrous mesothelioma involving left hemithorax. (*B*) Resected specimen demonstrates capsule on outer surface (upper) and the lobulated texture of the cut surface (lower). This patient lived 7 years after enucleation of tumor without evidence of recurrence.

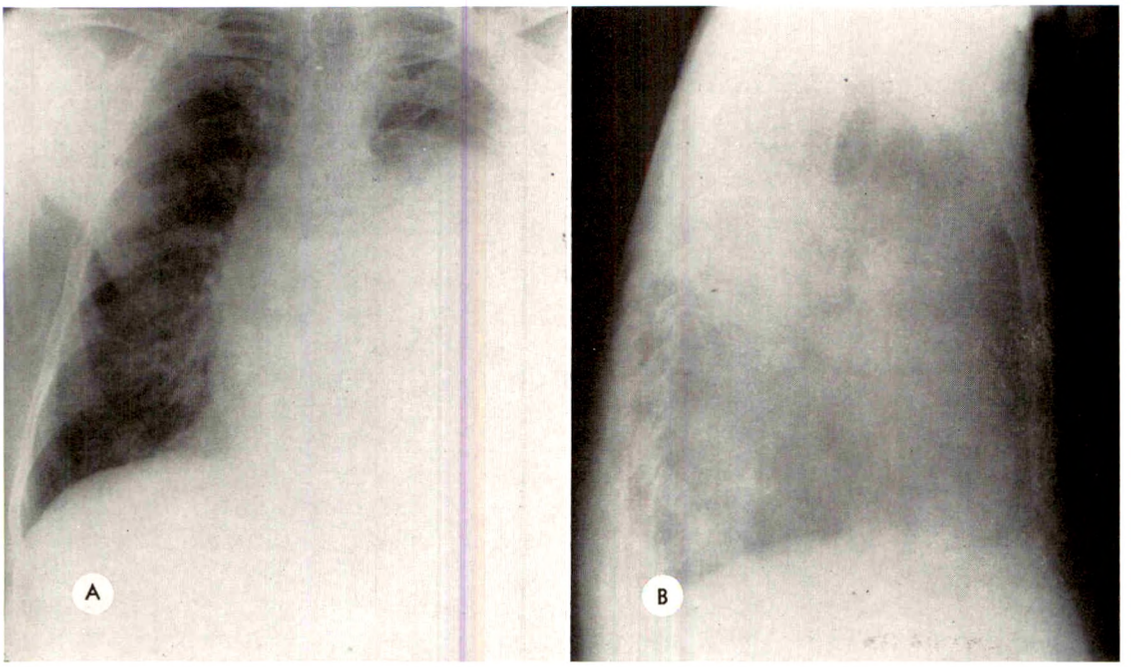


FIG. 17. (*A* and *B*) Chest roentgenograms illustrating a left pleural effusion in a 69 year old man with an epithelial mesothelioma. No mass is apparent in left hemithorax.

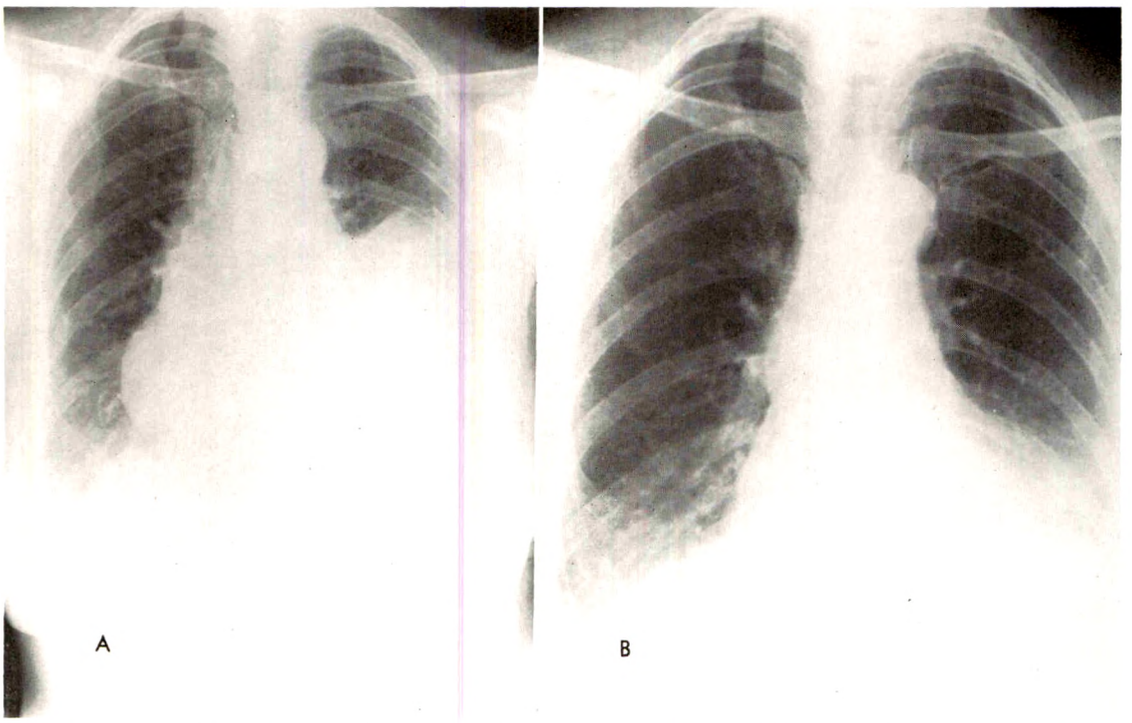


FIG. 18. (*A*) Chest roentgenogram of a 61 year old woman with an epithelial mesothelioma involving the left hemithorax associated with a massive pleural effusion. (*B*) No tumor was visible in left hemithorax after thoracentesis. Complete removal of pleural fluid was seldom possible.

fibrosarcomatous mesotheliomas developed pleural effusions at some time during their illness (Fig. 19, *A* and *B*).

THORACENTESIS AND CYTOLOGY OF FLUID

Benign Tumors. None of the patients with benign tumors had pleural effusions.

Malignant Tumors. Twenty-seven of the 31 patients with malignant tumors developed pleural fluid during their illness, and 22 of these patients had one or more thoracenteses. The fluid was usually serous or serosanguineous, but in a few instances it was frankly bloody. Cytologic examinations were done on the fluid from 20 patients, and cancer cells were identified in 9 of the 11 epithelial and 6 of the 9 fibrosarcomatous mesotheliomas examined (Fig. 20, *A*, *B* and *C*). The specific diagnosis of mesothelioma was not made unequivocally on pleural fluid cytology alone, but in a few cases it was strongly suspected and tissue biopsy was requested for confirmation. The cytologic pattern of mesothelioma in effusion has been well described by Klempman,[8] Naylor,[14] and Koss,[9] and our findings were in accord with their descriptions.

CYTOLOGY OF SPUTUM AND BRONCHIAL ASPIRATE

Cytologic examinations were performed on sputum or bronchial aspirate from 2 of the 6 patients with benign tumors and 15 patients with malignant tumors. No malignant cells were found.

BRONCHOSCOPY (ENDOSCOPY)

Benign Tumors. Two patients with benign tumors were bronchoscoped. Neither showed any abnormality.

Malignant Tumors. Fifteen patients with malignant tumors had bronchoscopic examinations. The bronchi were deviated or slightly distorted in a few patients, presumably from extrinsic pressure by tumor, but no significant endobronchial disease was seen.

One patient had esophagoscopy because of dysphagia, and partial obstruction from extrinsic pressure was found at the level of the diaphragm.

PLEURAL NEEDLE BIOPSY

Benign Tumors. Pleural needle biopsy was attempted in 4 of the cases with a benign mesothelioma, and it was inadequate for diagnosis in every instance.

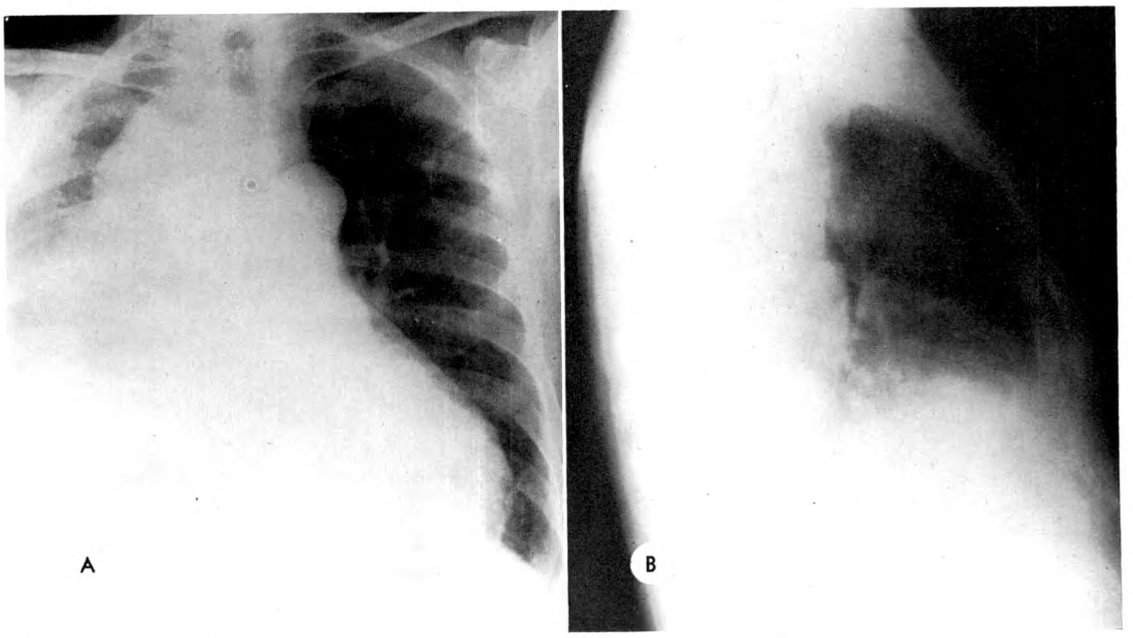


Fig. 19. (*A* and *B*) Chest roentgenograms of a 70 year old man with a fibrosarcomatous mesothelioma presenting as a large mass with effusion in the right hemithorax.

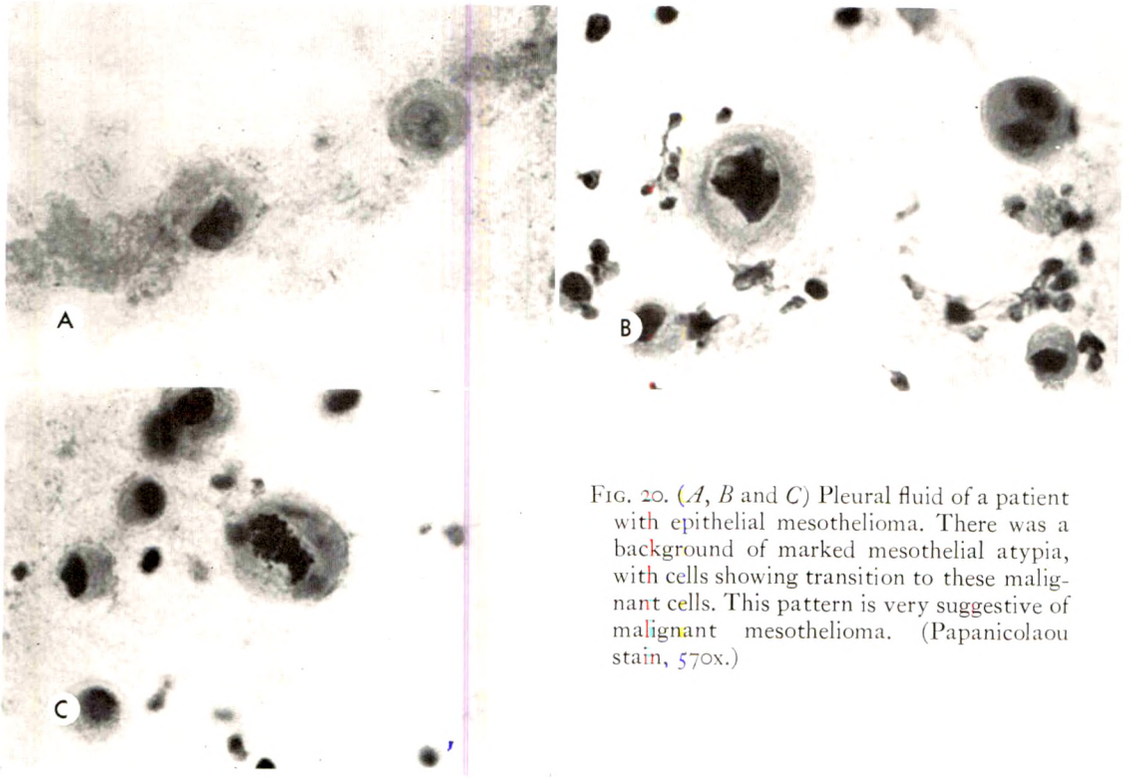


Fig. 20. (*A*, *B* and *C*) Pleural fluid of a patient with epithelial mesothelioma. There was a background of marked mesothelial atypia, with cells showing transition to these malignant cells. This pattern is very suggestive of malignant mesothelioma. (Papanicolaou stain, 570x.)

Malignant Tumors. Pleural needle biopsy was attempted in 9 cases with malignant tumor, and in 1 it was diagnostic of an epithelial mesothelioma. The remaining 8 biopsies were inadequate.

SCALENE LYMPH NODE BIOPSY

Bengin Tumors. None of the patients with benign tumors had scalene lymph node biopsy.

Malignant Tumors. Most of the patients had normal supraclavicular lymph node areas by physical examination early in their illness, and those who did later develop palpable lymph nodes were usually already known to have mesothelioma. Three patients with malignant mesotheliomas had a scalene lymph node biopsy as a diagnostic procedure before the nature of their illness was known; 2 of them had palpable supraclavicular lymph nodes. One of the patients with palpable lymph nodes was found to have metastatic malignant tumor, but the exact classification was uncertain until subsequent thoracotomy identified an epithelial mesothelioma in the contralateral hemithorax. No tumor was found in the scalene lymph node biopsies from the other 2 patients.

THORACOSCOPY

Benign Tumors. Thoracoscopy was not done on any patient with a benign tumor.

Malignant Tumors. Thoracoscopy was done on 2 patients with malignant tumors. In 1 case the examination was satisfactory and the tumor was well visualized, but the biopsy through the thoracoscope was unsatisfactory and thoracotomy was necessary. In the second case, bloody pleural fluid prevented adequate visualization of the tumor, and the thickened pleura interfered with movement of the thoracoscope.

PULMONARY FUNCTION STUDIES

Benign Tumors. The 2 patients with cellular fibrous mesotheliomas had large tumors and both had depressed pulmonary function. Only 3 of the 4 patients with sclerosing fibrous mesotheliomas were

tested and they all had normal pulmonary function.

Malignant Tumors. Twelve patients with malignant tumors were examined and all had depressed pulmonary function. Eight of these patients had epithelial mesotheliomas and 4 had fibrosarcomatous mesotheliomas.

METHOD OF ESTABLISHING THE CORRECT DIAGNOSIS

Benign Tumors. Thoracotomy was required to make the correct diagnosis in all 6 patients with benign tumors.

Malignant Tumors. Thoracotomy was required to make the correct diagnosis in 27 patients; Vim Silverman needle biopsy was diagnostic in 1 patient. Postmortem examination established the correct diagnosis in the remaining patients with malignant mesotheliomas.

TREATMENT AND RESULTS

BENIGN TUMORS

All of the patients with benign mesotheliomas were treated successfully by surgical excision of their tumors.

The 2 cellular fibrous mesotheliomas were both very large, filling most of the hemithorax, yet they were "shelled out" easily at thoracotomy (Fig. 16, *A* and *B*). One patient subsequently lived for 7 years without evidence of recurrence, and died of heart disease; the other is alive and well after 10 years.

The 4 patients with sclerosing fibrous mesotheliomas were all treated by simple excision of their tumors, either by transecting the pedicle and adhesions or by enucleation, and all are alive without recurrent tumor from 3 to 11 years later (Fig. 21, *A*, *B* and *C*).

MALIGNANT TUMORS

All treatment modalities failed for every case of malignant mesothelioma.

Epithelial Mesothelioma. Fifteen of the 16 patients with epithelial mesothelioma died of their disease in from 11 to 58 months following onset of symptoms. The average length of survival was 21 months; the median survivor lived 19 months. Survival from the beginning of therapy ranged from 2 to 55 months, and averaged 14 months; the median survivor lived 10 months following treatment. The 1 patient still alive has uncontrolled tumor 16 months after diagnosis.

Thoracotomy was carried out in 14 patients, but curative resection was attempted only in 4. Nine patients had pleural biopsy only, and 1 had partial excision of tumor. The 2 patients who did not have thoracotomy were diagnosed by Vim Silverman needle biopsy and by autopsy.

The 4 resections that were considered potentially curative were "complete" pleurectomy in 3 patients and extrapleural pneumonectomy in 1 (Fig. 22, *A*, *B* and *C*). The longest survivor had bilateral pleurectomies 2 years apart, and lived 55 months. She had no radiation therapy, and no chemotherapy until death was imminent. The patient treated by extrapleural pneumonectomy had had preoperative and postoperative radiation therapy, and lived only 5 months following surgery. The 2 remaining patients lived 2 months and 21 months respectively, after pleurectomy.

Twelve patients were treated by irradiation postoperatively, 1 was treated preoperatively and postoperatively, and 1 patient was treated following needle biopsy without thoracotomy. The tumor doses given varied from 2,000 r to 6,000 r, and were administered with 250 kv., 1 mev., 2 mev. and Co^{60} irradiation. Two patients had intrapleural radioactive gold, in 1 case in addition to external radiation therapy; and 1 patient had irridium 192 needles inserted into the tumor in addition to external irradiation. One patient with ascites had intraperitoneal radioactive phosphorus.

Chemotherapy was attempted in only 3 patients, and late in the course of their disease. The drugs used were chloroquine phosphate, nitrogen mustard and 5-fluorouracil. None had any appreciable effect.

Fibrosarcomatous Mesothelioma. All 15

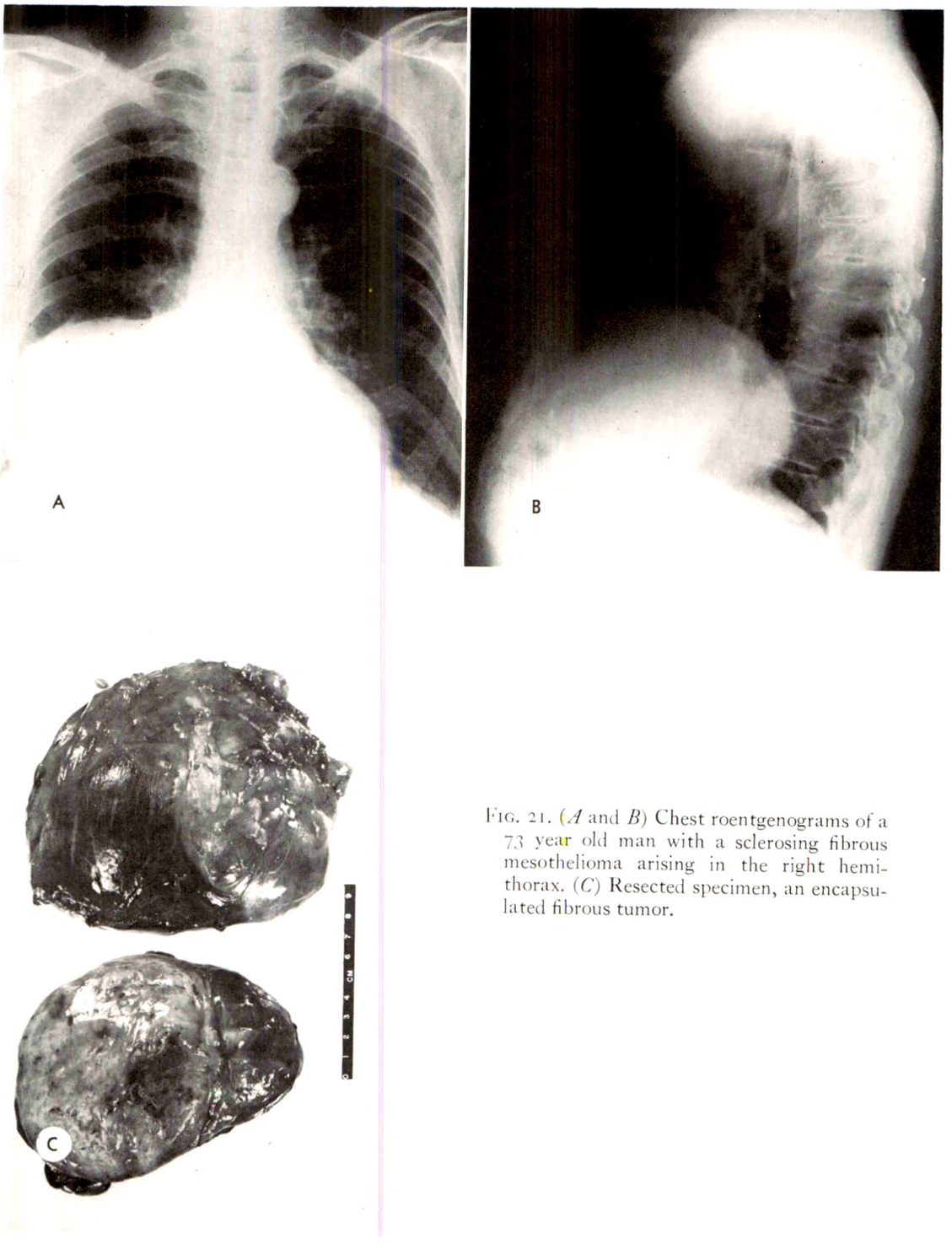


FIG. 21. (*A* and *B*) Chest roentgenograms of a 73 year old man with a sclerosing fibrous mesothelioma arising in the right hemithorax. (*C*) Resected specimen, an encapsulated fibrous tumor.

patients died of their disease within 3 to 82 months following onset of symptoms. The average length of survival was 19 months; the median survivor lived 13 months. The average length of life from the beginning of therapy was 14 months, and ranged

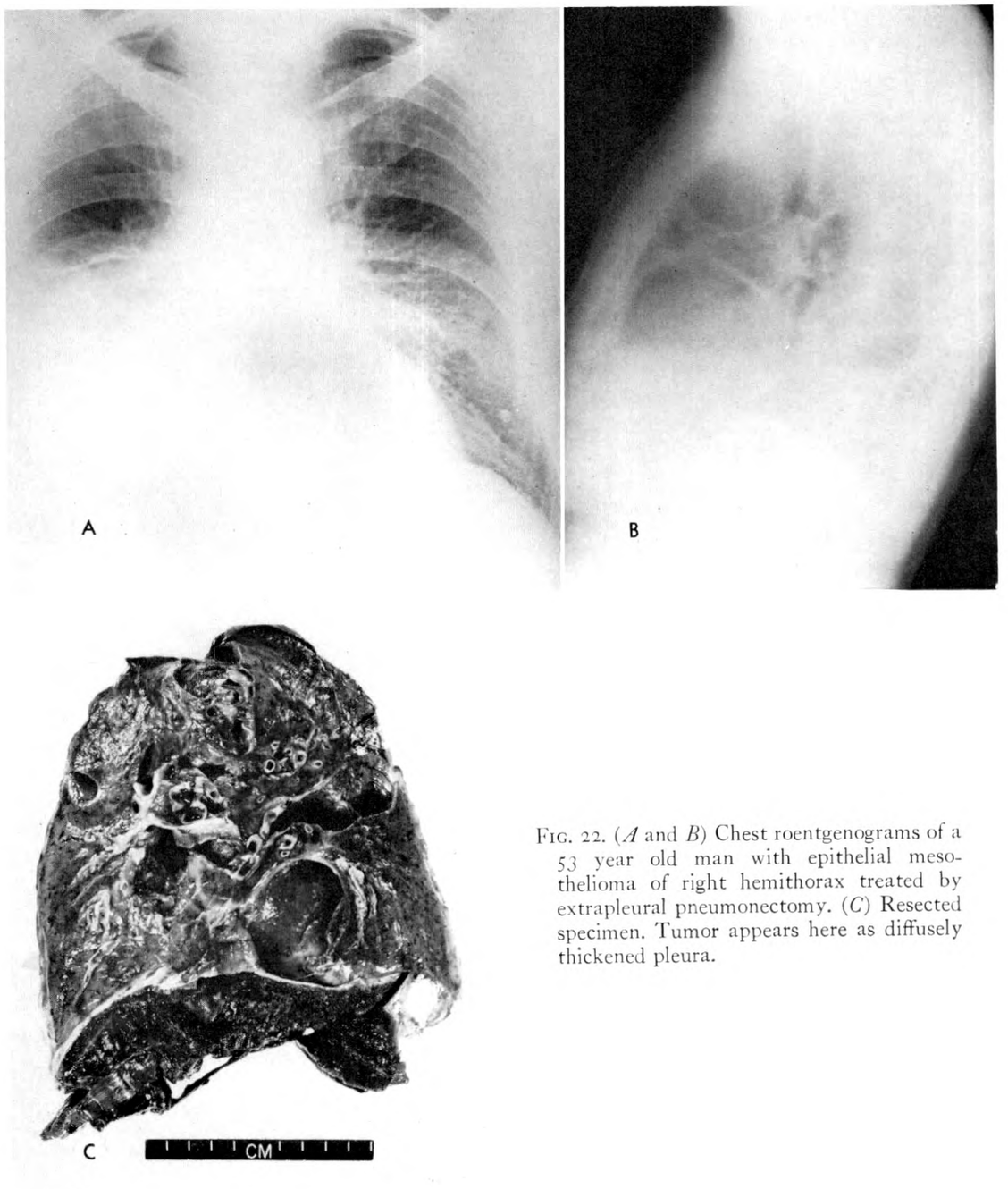


FIG. 22. (*A* and *B*) Chest roentgenograms of a 53 year old man with epithelial mesothelioma of right hemithorax treated by extrapleural pneumonectomy. (*C*) Resected specimen. Tumor appears here as diffusely thickened pleura.

from zero (postoperative death) to 82 months. The median survivor lived 9 months following treatment.

Thirteen patients had thoracotomy; the 2 other patients came to autopsy without specific diagnoses. Pleural biopsy was performed in 7 cases, partial excision of tumor in 3, excision of tumor with lobectomy in 2, and pneumonectomy with partial resection of diaphragm and excision of retroperitoneal tumor extension in 1 patient (Fig. 23, *A–D*). The last 3 patients were considered to have had potentially curative surgery. The patient treated by pneumonectomy

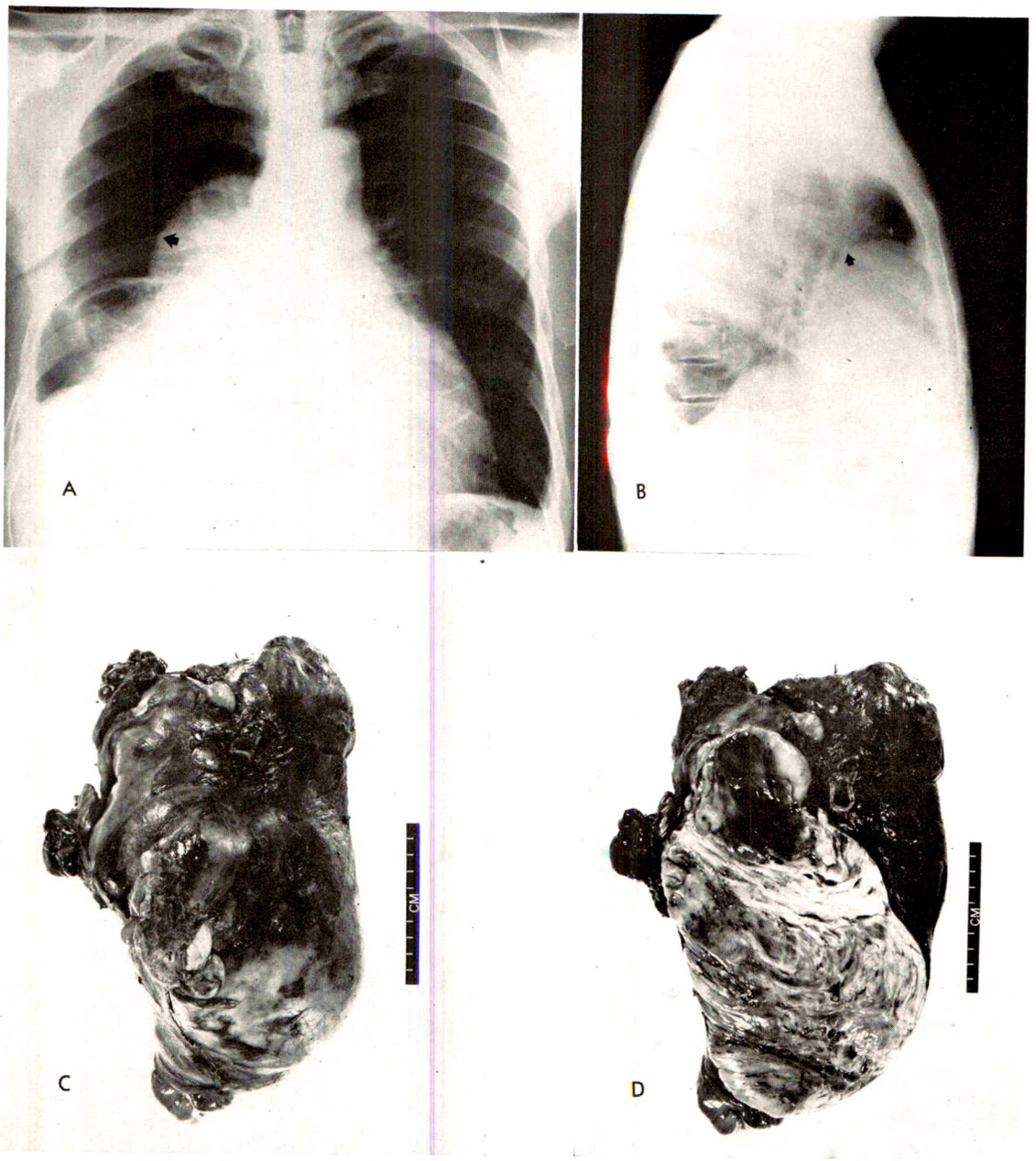


Fig. 23. (*A* and *B*) Chest roentgenograms of a 54 year old man with a fibrosarcomatous mesothelioma of the right hemithorax which invaded the diaphragm and retroperitoneal space. (*C* and *D*) Resected specimen. This patient died 24 hours postoperatively.

with radical excision of tumor died 1 day postoperatively. The 2 other patients both received radiation therapy and chemotherapy postoperatively, and survived 18 and 23 months, respectively.

Thirteen patients received some form of radiation therapy. Eleven were treated with tumor doses ranging from 1,200 r to 5,000 r, administered with 250 kv., 1 mev., 2 mev. or Co^{60} irradiation. Two patients had radon seeds implanted into their tumors at the time of surgery, and 1 subsequently had intrapleural radioactive gold instillation. The longest survival, 82

months, was achieved by partial excision of the primary tumor, immediate postoperative irradiation to the residua, and subsequent irradiation to areas with metastases.

Chemotherapy was used in 6 patients, but only late in their disease. Cyclophosphamide, 5-fluorouracil, nitrogen mustard, actinomycin D and methotrexate were the drugs tried. None had any significant effect.

SUMMARY AND CONCLUSIONS

1. Thirty-seven cases of mesothelioma from Memorial and James Ewing Hospitals were reviewed. They were classified according to gross and microscopic morphology as follows: benign fibrous mesotheliomas—cellular, 2 cases, sclerosing, 4 cases; and malignant mesotheliomas—epithelial, 16 cases, fibrosarcomatous, 15 cases. The validity of this classification was confirmed by the close correlation with clinical behavior.

2. Most of the patients were in their 6th and 7th decades; only 1 patient with a malignant epithelial mesothelioma was less than 45 years old, but nearly half the patients with fibrosarcomatous mesotheliomas were less than 35 years old and 3 were less than 20 years old.

3. Two-thirds of both the benign and malignant tumors were on the right side.

4. One patient with an epithelial mesothelioma had worked in an asbestos factory for 15 years and 3 others were employed in the construction industry where exposure to asbestos might have occurred. None of the other patients was known to have been exposed to asbestos. Asbestos bodies were found in pathologic specimens from only 2 cases, 1 with an epithelial and 1 with a fibrosarcomatous mesothelioma, and neither had known exposure to asbestos.

5. The patients with benign fibrous mesotheliomas were essentially asymptomatic. They all presented with intrathoracic tumor masses that were discovered incidentally by chest roentgenography.

6. The most common symptoms of patients with malignant mesothelioma were chest pain, dyspnea and cough. The most common finding by chest roentgenography was pleural effusion, which was present in virtually all of the patients with epithelial mesothelioma and more than half the patients with fibrosarcomatous mesothelioma.

The combination of chest pain and pleural effusion appears to be particularly significant, and of itself should suggest the possibility of mesothelioma. Unlike the pleuritic pain of inflammatory origin, which usually subsides with effusion, the pain of malignant mesothelioma gradually increases despite the effusion.

7. Thoracotomy with pleural biopsy or resection of tumor was required for diagnosis of all patients with benign mesothelioma, and 27 of the 31 patients with malignant mesothelioma. Diagnosis in the remaining patients was made once by needle biopsy and on 3 occasions at autopsy.

8. The most useful diagnostic laboratory procedure, short of biopsy, was cytologic examination of the fluid obtained by thoracentesis. Cancer cells were identified in specimens from 15 of the 20 patients with malignant mesothelioma who had such examinations performed. In a few cases, the specific possibility of mesothelioma could be suggested.

We have never found cancer cells in the sputum or bronchial aspirate of patients with mesothelioma though they would be expected from over 80 per cent of all patients with primary lung carcinoma and 50 per cent of patients with pulmonary metastases.[10] Thus, mesothelioma should be strongly suspected in patients without a known site of primary cancer elsewhere when they present with effusion that contains cancer cells and do not have cancer cells present in repeated specimens of sputum. Certainly no patient with pleural effusion containing cancer cells of undetermined origin should be automatically assigned to the category of inoperable bronchogenic carcinoma.

9. All of the patients with benign fibrous mesothelioma were treated by surgical ex-

cision, and all appear to have been cured.

10. All treatment modalities failed to cure any case of malignant mesothelioma. Symptomatic relief of dyspnea early in the disease was obtained by removal of fluid through thoracentesis or by pleurectomy, irradiation or intrathoracic chemotherapy. No one method was more effective than another. Dyspnea late in the disease was due primarily to compression of the lung by tumor and was refractory to treatment.

11. It is our belief that the fibrosarcomatous mesotheliomas arise from the connective tissue stroma of the pleura, as proposed long ago by Klemperer and Rabin.[7] They might best be termed pleural fibrosarcomas but it is customary to consider them as mesotheliomas, and we accept this designation which has the merit of grouping together tumors with many clinical features in common. We are aware of the tissue culture work of Maximow[12] and of Stout and Murray[20] suggesting that normal mesothelial cells and cells from epithelial mesotheliomas are capable of transformation into fibroblasts. This may well explain the tendency toward spindle metaplasia in some epithelial mesotheliomas (a type of metaplasia that is not uncommon, incidentally, in many other epithelial tumors), but it does not justify the assumption that all malignant pleural tumors arise from surface mesothelial cells. On the contrary, it seems unreasonable to assume that in this one location only (the pleura) connective tissue is incapable of giving rise to malignant tumors. Confirmation of the work by Maximow and by Stout and Murray with modern techniques of tissue culture would be highly desirable. None of the tumors classified here as fibrosarcomatous mesotheliomas had an epithelial component, and none had demonstrable origin from surface mesothelial cells.

12. The frequency of metastases from malignant mesotheliomas to regional lymph nodes, to the opposite lung, and to distant sites was of some interest to us. We found metastases much more common than was expected. It may be that overly restrictive criteria for diagnosis of mesothelioma at autopsy have specifically excluded some cases simply because other organs were involved.[22]

Multiple peritoneal tumor implants, and pleural implants as well, were found only in patients with epithelial mesotheliomas. We have been unable to determine whether they do, in fact, represent metastases, or are an expression of multifocal origin. The answer to this question obviously has considerable bearing on the clinical problems of treatment.

13. A significant number of the patients died from cardiorespiratory failure, with or without superimposed infection, because of local enlargement of the tumors causing lung compression and interfering with cardiac action. Several of these patients had clinical and autopsy confirmation that the tumor was confined to the chest. Most frequently, this was seen in older patients with fibrosarcomatous mesothelioma. Repeat pleurectomy may offer significant palliation for some of these patients, but the technical hazards of the procedure must be seriously considered before recommending it in any specific case.

It is the apparent localization of this disease, even when the cancer is advanced, that makes the management of these patients heartbreaking. Possibly newer methods of patient support during surgery will allow more extensive procedures, and possibly this will allow some patients to be cured. Until the solution is found, all possible treatment modalities which offer some hope are justified.

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VOL. 99, No. 4

RADIOLUCENT INTRACAVITARY RADIATION APPLICATORS*

THEIR SPECIAL USEFULNESS IN COMPUTER CALCULATED DOSIMETRY

By IRVING J. WEIGENSBERG, M.D., JOHN R. MARSHALL, M.D., *and* WILLIAM E. POWERS, M.D.

DOSAGE calculation of interstitial and intracavitary radiation sources has been difficult, laborious, and inaccurate; however, with modern electronic computer techniques, this need no longer be true. It is now possible and practical to calculate the precise dose at thousands of points about an implant, and to meaningfully display the attendant three dimensional dose distribution patterns.[1,8,15,17]

Fundamental to such calculations is knowledge of the exact spatial location of the radiation sources. While available roentgenographic techniques readily locate the applicators, the radiopacity of the commonly used metallic applicators frequently prohibits precise localization of the actual sources. Without this information, accurate computer dosimetry is impossible.

Radiolucent plastic applicators permit clear, precise visualization of the actual radiation sources, and, therefore, combine with modern computer technology to provide detailed and accurate dosimetry for complex implantations.

METHODS

The methods of calculating dose distribution by electronic computers have previously been described.[1,15,17] Stereoscopic or orthogonal roentgenograms can be used to localize the sources and assign them spatial coordinates.[15] On the basis of these coordinate data, the dose contribution to a multitude of points from each source is computed electronically and the resultant dose distribution recorded.

The radiolucent plastic applicators have the same external configuration and dimensional stability as the usually employed metal applicators, and, except for the absence of metal, they are virtually identical. Lucite, nylon or teflon have all proven to be satisfactory, but Lexan* may be the optimal material. This plastic is said to provide maximum resistance to the damaging effects of both irradiation and sterilization with benzalkonium chloride.[9] Some plastic applicators are commercially available;† others must be specially made. Because most of these are simple to fabricate, they can be manufactured locally. They can thus be readily modified in dimension and contour as needed or desired by the therapist and the circumstances of an individual case.

RESULTS

The clarity of source visualization with the plastic applicators is shown by the roentgenogram in Figure 1. In the top row are the usual metal models, while below are the comparable ones made of radiolucent plastic. The separation of adjacent sources by small plastic spheres or disks further improves delineation of the source ends.

Figure 2 illustrates the spatial similarity of the metal and plastic Heyman or Campbell intrauterine capsules. The small capsules are 25×6 mm. in external dimensions, and the large capsules are 25×10 mm. Either capsule may be obtained with internal dimensions suitable for most commonly

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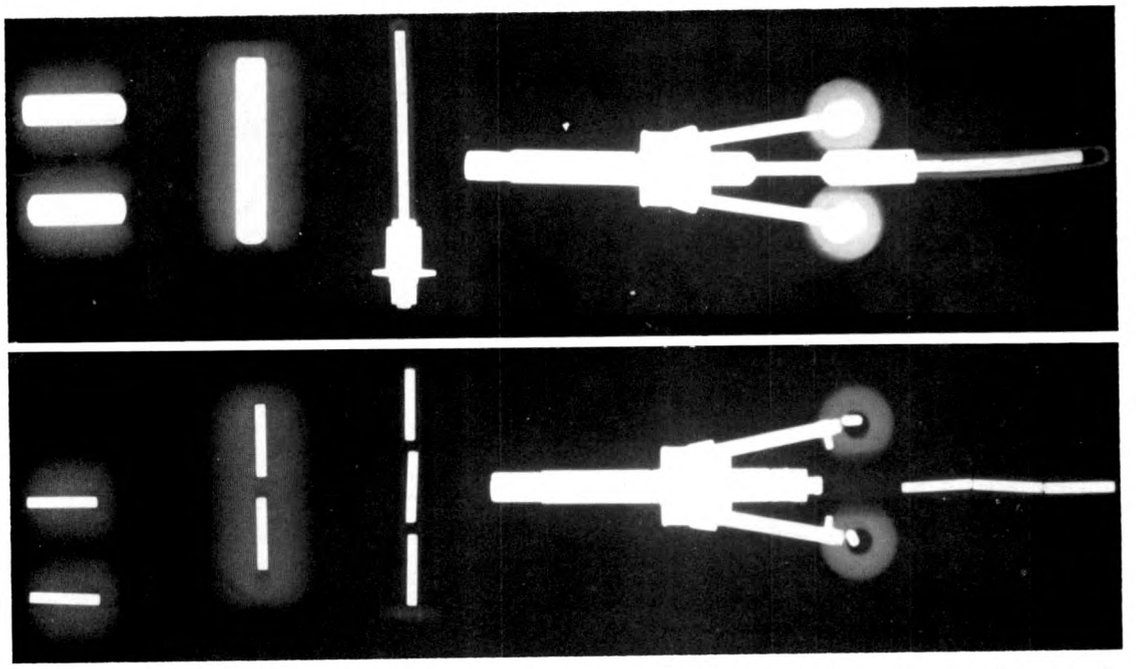


FIG. 1. Roentgenogram of metal and plastic applicators showing improved source visualization with the plastic applicators. *Top row.* Usual metal applicators: vaginal ovoids, a two cell vaginal cylinder, a three cell intrauterine tandem, and a Ter Pogossian applicator. *Bottom row.* Same applicators in radiolucent plastic with small plastic disks or spheres separating sources in tandem.

used radium or cobalt 60 sources. All capsules fit the usual inserters. Such nylon capsules were first described by Kraemer and Lewis[7] but were advocated for their economy, not their radiolucency.

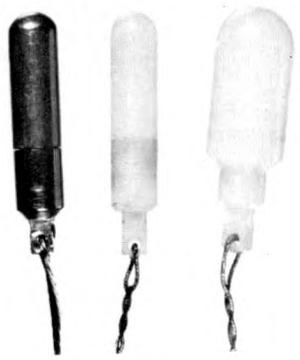


FIG. 2. Metal and plastic Heyman–Campbell intrauterine applicators showing similarity of form. Small capsules are of 25×6 mm. external dimensions, large capsule of 25×10 mm. Either capsule may be obtained with internal dimensions suitable for most commonly used radium or cobalt 60 sources. All capsules fit the usual inserters.

The advantages of utilizing the radiolucent plastic applicators and the precise computer dosimetry which they make possible is demonstrated by the following 4 actual patient implantations.

Figure 3 is a roentgenogram of an implant for recurrent squamous cell carcinoma of the vagina and labium. The metal of the vaginal cylinder obscures not only the sources contained within but also 2 of the interstitial needles and makes computer dosimetry impossible. A similar implant using radiolucent applicators is shown in Figure 4. Each source is well visualized. Computer calculation of dose distribution provides an accurate estimation of tissue radiation as shown in Figure 5. The isodose curves represent the indicated thousands of roentgens. The planes of computation are those indicated in Figure 4. The points where the sources pierce the planes of computation are represented by dots.

Intrauterine application of the usual metal Heyman or Campbell capsules prohibits actual source identification and

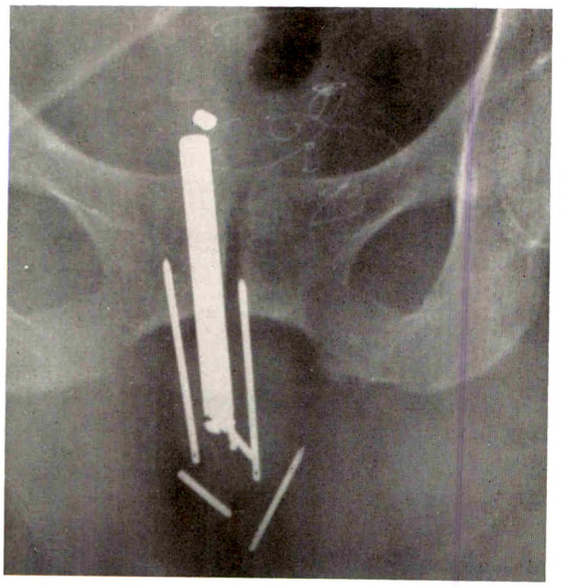


Fig. 3. Roentgenogram of an implant for recurrent squamous cell carcinoma of the vagina and labium. The metallic portion of the vaginal cylinder obscures not only the sources contained within but also 2 of the adjacent interstitial needles. The ovoid opacity at the cephalic end of the cylinder is a radiopaque marker on the cervix.

renders computer dosimetry impossible. A typical application using metallic capsules and additional vaginal vault irradiation is shown by the roentgenogram in Figure 6.

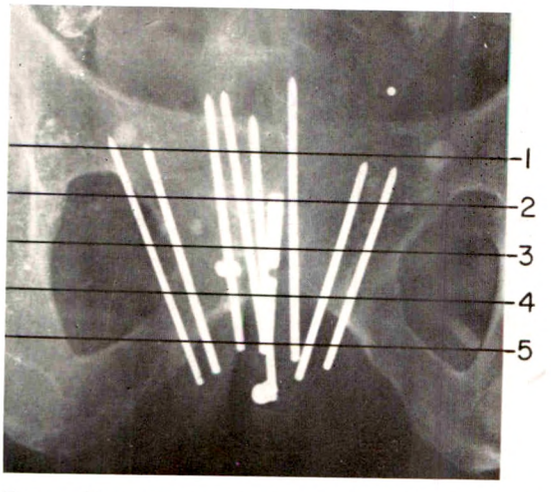


Fig. 4. Roentgenogram of an implant similar to the one in Figure 3 except that a radiolucent plastic vaginal cylinder was used. Note the distinct delineation of all the sources in this complex array. The planes of isodose computation are indicated.

The capsules obscure one another, identification of the individual applicators is difficult, and no actual sources are visible. A similar application using 6 radiolucent plastic intrauterine capsules, a plastic tandem containing 2 sources in the cervical canal, and plastic Manchester ovoids in the fornices is shown in Figure 7. The individual sources are clearly seen. Computer calculated dose distributions for the planes indicated in the roentgenogram are shown in Figure 8. Here we have information concerning dosage, not only to various portions of the uterus, but also to many other points of interest in the parametria, rectum, and bladder.

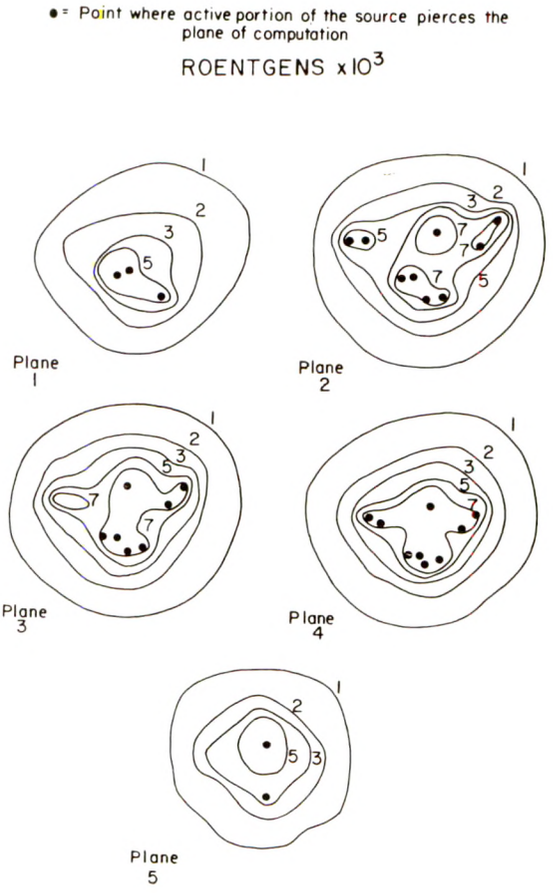


Fig. 5. Computer calculated dose distribution for the implant illustrated in Figure 4. The numbered isodose curves indicate thousands of roentgens. The planes of computation are as indicated in Figure 4.

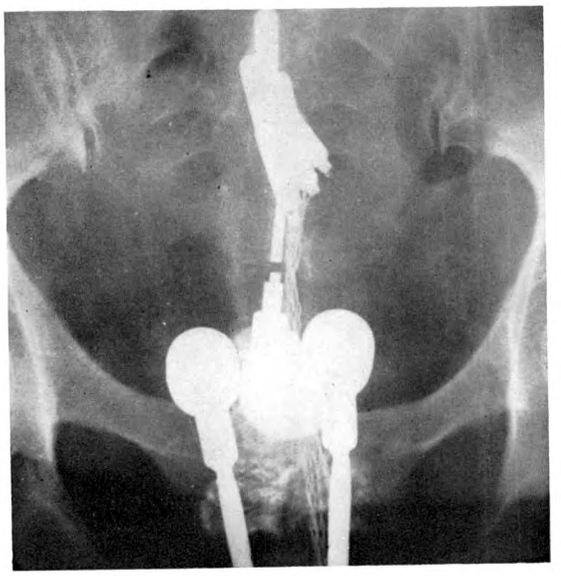


FIG. 6. Roentgenogram of multiple capsule intracavitary implant for endometrial adenocarcinoma employing metal applicators. Individual sources are not visible.

DISCUSSION

Radiotherapy began as an empiric art, and the continued use of milligram hours as a quantitative measure of radiation reflects this past. Although clinical dosimetry for complex implantations has been difficult, several techniques have been developed in an attempt to provide more rational therapy. Some investigators have used measurements about simulated implants in phantoms.[5,6,12] Others have preferred fewer measurements taken directly from the patient and have inserted measuring devices into adjacent hollow viscera such as the bladder or rectum.[11] Laborious manual calculations have also been employed to determine the dose at a relatively small number of points of interest.[4,8,10,15,16] Nevertheless, none of these approaches provides accurate and comprehensive dosimetry for a unique and specific array of sources in a particular patient.

However, such rapid, accurate, and comprehensive individual patient dosimetry is now possible. Radiolucent plastic ap-



FIG. 7. Roentgenogram of multiple capsule intracavitary implant for endometrial adenocarcinoma utilizing radiolucent plastic applicators. The individual sources are clearly visible. The planes of isodose computation are indicated.

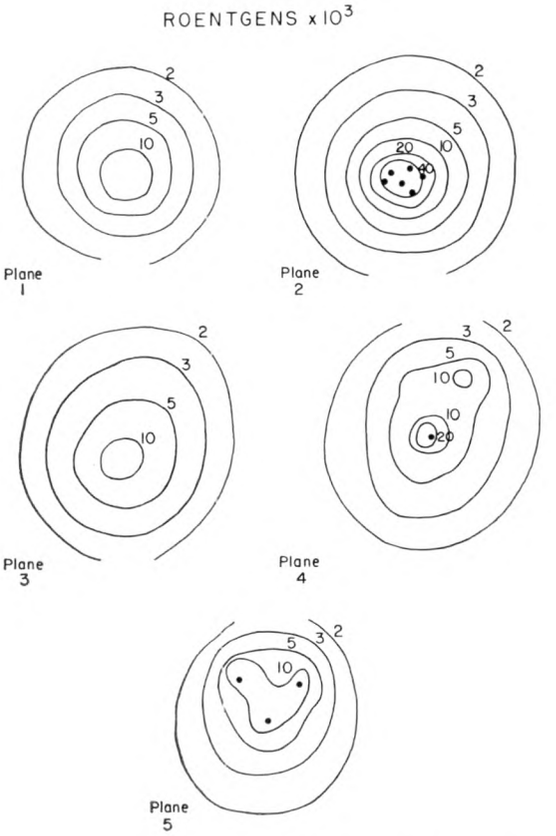


FIG. 8. Computer calculated dose distribution for the implant illustrated in Figure 7. The numbered isodose curves indicate thousands of roentgens. The planes of computation are as indicated in Figure 7.

plicators permit clear, precise visualization and localization of the actual sources. Virtually unlimited and economical calculation by computer, when combined with this exact source localization, provides accurate, three dimensional, isodose curves for even the most complex implantations. Gross approximations are no longer acceptable where accurate dosimetry is required.

SUMMARY

Recent developments in computer techniques make available accurate and clinically useful calculations of dosage distribution about interstitial and intracavitary implants. Metallic applicators interfere with the precise localization of the radiation sources required for the utilization of these techniques. The use of radiolucent plastic applicators permits clear, precise visualization and localization of the individual sources. These applicators combine with modern computer technology to provide detailed and accurate three dimensional dosimetry for complex implantations.

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INTRA-ARTERIAL 5-BROMODEOXYURIDINE AND X-RAY THERAPY*

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IN SPITE of the substantial radiobiologic evidence for the efficacy of some halogenated pyrimidines as radiosensitizing agents, rigorous clinical confirmation of radiosensitization has not been achieved. Greer and Zamenhof[11,12] first demonstrated an increase in the sensitivity of *E. coli* to ultraviolet radiation following the incorporation of 5-bromouracil (BU) into the DNA of the organism. Djordjevic and Szybalski[5] observed an increase in sensitivity to both x-ray and ultraviolet irradiation when mammalian cells were pretreated *in vitro* with 5-bromo-2′-deoxyuridine (BUdR). Kaplan, Smith, and Tomlin[18] observed sensitization of bacteria to x-rays after BU incorporation. Increase in radiosensitivity of cells grown *in vitro* has also now been produced with 5-chlorodeoxyuridine (CUdR),[8] 5-bromodeoxycytidine (BCdR),[1,21] 5-iododeoxyuridine (IUdR) and 5-iododeoxycytidine (ICdR).[9] In all instances of radiosensitization by halogenated pyrimidines, the degree of radiosensitivity has been shown to be a function of the degree of replacement of the normal base, thymine in the DNA of the cells of the sensitized tissue by the halogenated analogue. Maruyama *et al.*[18] and Berry and Andrews[2] demonstrated radiosensitization *in vivo* when ascites tumor cells were pretreated with the halogenated nucleosides. A more comprehensive review has recently been prepared by Doggett *et al.*[6]

Limited clinical trials with BUdR and IUdR in combination with radiation have been reported. In an uncontrolled study, Krant *et al.*[14] treated 14 patients with intravenous BUdR and irradiation and thought that they observed some increase in radiation response, although Kriss and co-workers[15,16] observed rapid debromidation of BUdR after intravenous injection both in rats and in man. Kriss *et al.* have shown more recently mean body retention of 24 per cent and 31 per cent of 2-C^{14}-BUdR and 2-C^{14}-BCdR by monitoring the $C^{14}O_2$ expired by patients given 30 minute intravenous infusions of BUdR or BCdR with the C^{14} labeled tracer. It is reasonable to assume that the retained labeled thymidine analogue is incorporated into the DNA of any tissue actively synthesizing DNA at the time. This suggests that the enzymatic process by which the analogues are catabolized, leading to debromidation, is less capable of handling larger doses, thus permitting analogue incorporation into DNA.[17] Fletcher *et al.*[10] treated 4 patients with advanced head and neck cancer and intra-arterial infusions of BUdR (40–48 mg./kg.) for 4 days prior to the administration of irradiation by cobalt 60 teletherapy (2,000 rads total in two 1,000 rad doses 7 days apart). In 2 patients, DNA extracted from tumor biopsies was subjected to centrifugation in a cesium chloride gradient. No incorporation of the BUdR into tumor DNA could be demonstrated.

Since 1961, we have been investigating

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combination therapy using various chemotherapeutic agents intra-arterially for advanced cancer of the head and neck and pelvis.[7] In 1964, BUdR for human use was supplied to us by the Cancer Chemotherapy National Service Center. Five patients were treated in a pilot study to determine the feasibility of using this drug. The first 3 patients received intra-arterial BUdR (250–500 mg./catheter) in 30 minute pulses b.i.d. the 48 hours preceding each x-ray treatment (500 rads every 3–4 days for 5–6 weeks). This plan allowed at least 1 day post irradiation for recovery of DNA synthesis and mitotic activity. The 2 other patients were given BUdR continuously throughout their course of irradiation after an initial loading dose of BUdR for 4 days. There were no serious untoward reactions encountered in these 5 patients, although the 3 who received 30 minute pulses of up to 500 mg. complained of facial pain during the drug infusion. Because methotrexate blocks the *de novo* synthesis of thymidine, it was decided to administer methotrexate prior to the BUdR in an effort to enhance its incorporation into tumor cells. The final experimental protocol is presented below.

PROTOCOL

Patients with advanced untreated epidermoid carcinoma of the head and neck (T_3-N_1, N_2,-N_3,-M_0 or T_4, -N_0, -N_1, -N_2, -N_3, -M_0) or patients with either Stage III or IV carcinoma of the cervix are admitted to the radiotherapy cancer research unit. A pretreatment evaluation is initiated and includes a routine admission work-up, evaluation of hepatic function, extensive roentgen examination of the primary region and likely metastatic sites, electrocardiogram, electroencephalogram and bacterial cultures of the mouth, nose and throat. Each patient is then assigned to one of three treatment plans by the cast of a die. The three possibilities include:

(A) Intensive radiation therapy alone (6,000 rads in 6 weeks at 200 rads daily to the primary and all positive lymph node regions);

(B) Arterial infusion of methotrexate (25 mg./catheter/day, and citrovorum factor, 6 mg. intramuscular q 6 hr. for 2 weeks followed by irradiation as in option A);

(C) Pre-irradiation arterial infusion with methotrexate as in option B, followed by pre-irradiation arterial infusion of BUdR (500 mg./catheter/day plus 25 microcuries 2-C^{14}-BUdR per catheter/day) administered for 4 days at the conclusion of the methotrexate infusion (loading dose).

In group (C) after the loading dose of BUdR, the drug is continued at 250 mg./catheter/day throughout the course of x-ray therapy or until excessive local reaction or a significant catheter complication dictates its discontinuation. In each patient the position of the catheter is frequently verified by fluorescein injection and ultraviolet illumination. Biopsies are obtained of both the neoplastic and regionally infused normal tissues after the 4 day loading dose with tagged BUdR. The tissue is submitted for biochemical determination of the 2-C^{14}-BUdR incorporation in the DNA of the biopsy specimen. Additional biopsies are obtained for bromine activation analysis and for radioautography. Frequent clinical examination of the patient, serial blood counts, hepatic function tests, and serum bromide levels are carried out.

CLINICAL OBSERVATIONS

All patients treated with BUdR and x-ray, irrespective of the methotrexate pretreatment, displayed intense local reactions both in the tumor and in the normal mucosa sharply restricted to the infusion bed. The earliest changes are manifest by erythema of the infused tissue within the same field of irradiation. The erythema was most easily detected on the dorsal surface of the tongue by an early effacement of the hypertrophied papillae of the tongue (furry tongue) often seen in patients with

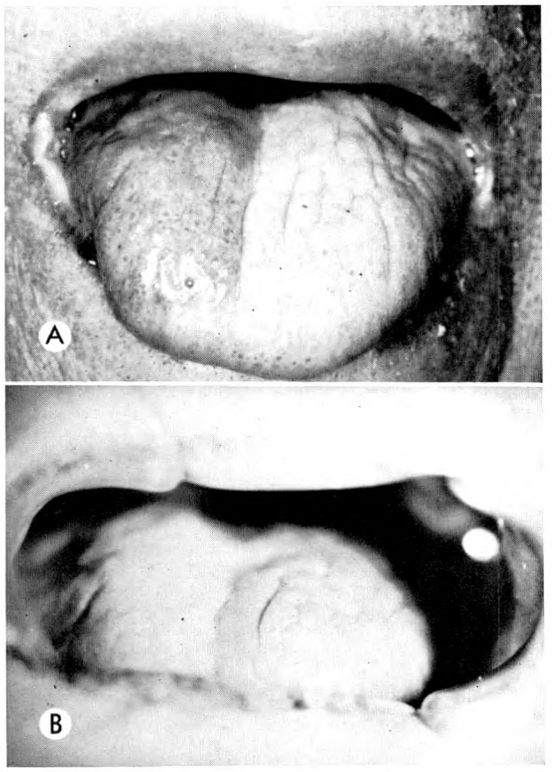


Fig. 1. (*A*) Early erythematous radiation reaction limited to right side of tongue after BUdR infusion into right carotid artery. Both sides of tongue received 1,000 rads. (*B*) Photograph exposed with ultraviolet light after fluorescein injection of right external carotid artery. Note limitation of fluorescence to right side of tongue.

advanced oral cancer. The hypertrophied papillae apparently desquamate, resulting in an atrophic, erythematous and somewhat painful mucosa (Fig. 1, *A* and *B*). Depapillation has also been observed with 6-mercaptopurine and seems distinctly different from the rather rapid development of the patchy membranous mucositis observed after intra-arterial methotrexate. Table 1 depicts the time course of the development of mucositis in the BUdR patients as compared to our previously reported series of patients treated with either methotrexate or 6-mercaptopurine administered concomitantly with x-ray. It is particularly notable that in the BUdR patients once mucositis developed it progressed rapidly through the patchy to the confluent stage. Asymmetric skin reactions were observed in 3 patients. In 2 a minimal increase in cutaneous erythema was noted within the radiation field on the infused side as compared to the contralateral skin which had received the same radiation dose. In 1 patient, however, this asymmetry of cutaneous reaction was particularly striking (Fig. 2, *A* and *B*). This patient received periodic irradiation at the rate of 500 rads skin dose every fourth day administered by opposed facial fields. At a skin dose of 5,500 rads, a

Table I

Local mucosal effects and dose/time factors in patients receiving chemical infusion and x-ray therapy for advanced head and neck tumors

Group	Pre 1964 MTX with X-ray (22 pt.)		Pre 1964 6-MP with X-ray (9 pt.)		A X-ray Alone (9 pt.)		Pilot BUdR with X-ray (5 pt.)		B MTX before X-ray*	C MTX before BUdR with X-ray (8 pt.)	
	Rads	Days	Rads	Days	Rads	Days	Rads	Days		Rads	Days
Onset Patchy Mucositis	1,700	13	2,430	20	3,200	23	2,320	18		2,230	17
Onset Confluent Mucositis	2,850	21	3,800	29	4,500	32	2,575	19		2,980	23
Average Total X-ray Dose and Treatment Time	6,310	46	6,510	43	6,360	45	5,900	47		6,340	57

* By chance, the number of patients allotted to Group B is as yet insufficient to be reported.



FIG. 2. (*A*) Skin of right side of face at 5,500 rads. Note minimal reaction. (*B*) Skin of left side of face at same radiation dose but with concomitant BUdR infusion. Note moist radioepidermatitis.

confluent moist radioepidermatitis appeared on the infused side whereas only minimal erythema of the contralateral skin was observed. Figure 3 demonstrates complete healing of the radioepidermatitis after 1 month. Epilation occurs consistently in the anatomic area of distribution of the infused external carotid artery. It was noted after about 3 weeks of BUdR infusion and is only temporary. Fletcher *et al.* observed alopecia in 1 of the 4 patients treated with intra-arterial BUdR and it was a consistent finding in the patients who received intravenous IUdR reported by Calabresi *et al.*[4]

A finding which we have not seen reported is the development of transverse furrows in the fingernails (Beau's lines). In contrast to the intravenous IUdR, we have not observed significant bone marrow depression (Table II). Peripheral white blood cell depression (as low as 3,000 white blood cells/cubic millimeter) occurred but this has been observed frequently in patients treated with x-ray alone. Similarly, the incidence of hepatic toxicity as manifest by at least two abnormal liver function tests other than bromsulphalein has been observed infrequently in contrast to our previous observations with methotrexate.

BIOCHEMICAL STUDIES

Biopsies of normal and neoplastic tissue were obtained from patients who had received BUdR labeled with C^{14} in the two position of the pyrimidine ring. One-hundred microcuries were mixed with the cold BUdR during the 4 day period of drug administration prior to the initiation of

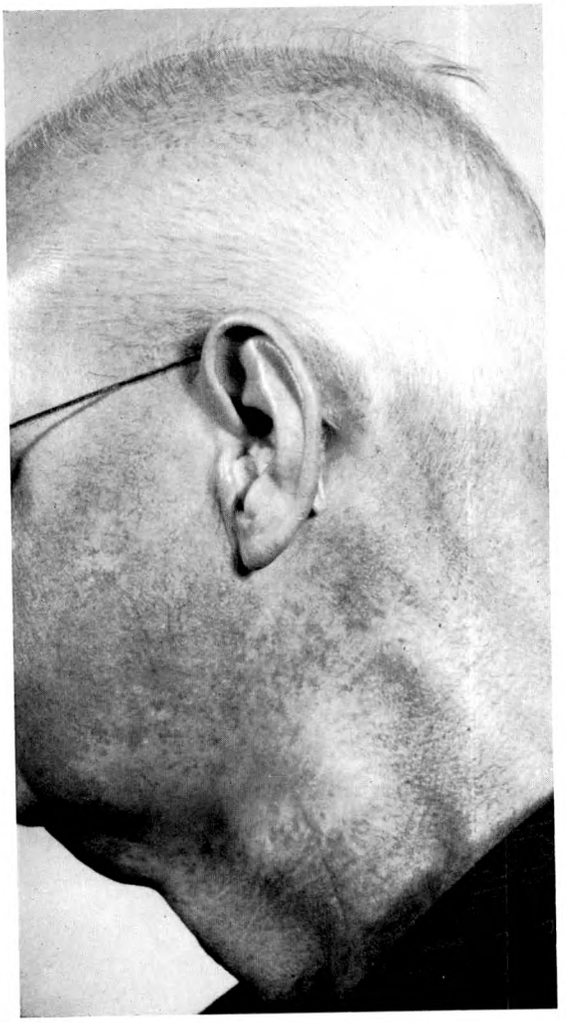


FIG. 3. Same patient as illustrated in Figure 2*B* but 1 month later, showing complete healing of the radioepidermatitis.

radiation therapy (loading dose). The biopsies were obtained at the conclusion of the loading dose and in 1 instance a second tracer dose of C^{14}-BUdR was administered after 1 month of therapy. In 5 patients, it was possible to determine the total radioactivity in the DNA of the specimen by the following method:

Total Radioactivity of Biopsy. Approximately 0.1 gm. of weighed tissue was extracted in 1 ml. of 0.5 *N* perchloric acid at 80°C. for 60 minutes. The solution was cooled, centrifuged to remove protein and a 0.5 ml. aliquot of the supernatant (containing the hydrolyzed nucleic acids) was counted in a liquid scintillation counter. A value for the μM of BUdR incorporated per gram of tissue was calculated (Table III) from the counts per gram of tissue and the specific activity of injected BUdR.

This determination indicates only the presence of C^{14} in the DNA of the biopsy and does not prove that the label is incorporated as BU. In general, sample sizes were too small to permit separation of the bases and positive identification of bro-

TABLE II

SYSTEMIC TOXICITY OF INTRA-ARTERIAL CHEMICAL AND X-RAY THERAPY OF PATIENTS WITH ADVANCED HEAD AND NECK CANCER

	MTX and X-ray (22 pt.)	X-ray Alone (9 pt.)	BUdR and X-ray (5 pt.)	MTX before BUdR and X-ray (8 pt.)
White Blood Cell Count				
3,000–4,000	12	4	4	4
2,000–3,000	8	—	2	2
under 2,000	—	—	—	—
Platelet Count				
100,000–150,000	7	1	1	—
50,000–100,000	2	1	—	—
under 50,000	—	—	—	—
Hematocrit				
under 30%	9	1	3	3
Hepatic Toxicity	11	—	2	4

TABLE III

Patient	Source of Sample	μM BUdR/gm. Tissue	Per Cent Thymine Replacement
B.S.	Tumor	0.145	4.9
A.C.	Tumor after BUdR alone	0.084	
	After FUdR+BUdR	0.129	
	A. Tumor after four 30 minute pulses of BUdR 12 hours apart (5 different samples from biopsy)	0.046	
P.C.	B. Tumor (second specimen obtained 96 hours after A)	0.032	
	C. Tumor (third specimen 1 month after continuous BUdR and X-ray therapy)	0.013	
E.S.	Tumor (multiple biopsies)		
	anterior	0.028	
	posterior	0.045	
	superior	0.025	
	inferior	0.024	
	center	0.034	
		0.031 Average	
L.L.	Normal tissue in infusion bed (histologically this proved to be mostly scar)	0.037	
	Tumor (multiple biopsies)		
		1. 0.134	
		2. 0.108	
		3. 0.131	
		0.124 Average	
H.S.	Tumor	*0.25	
J.L.	Tumor	*1.0	

* The BUdR concentrations were calculated from the amount of tissue bromine which was determined by neutron activation analysis. The neutron activation analyses were performed through the courtesy of W. F. Bethard, M.D., General Atomic, San Diego, California. The unfixed biopsy specimens were irradiated in a Triga reactor. They were allowed to set for 6 days to permit decay of Na^{24} and Cl^{38} and then counted in a gamma-ray spectrometer.

mouracil. In 1 patient, however, sufficient DNA was recovered to permit base analysis by the following procedure:

Per Cent Replacement of Thymine by Bromouracil. DNA was isolated from about 0.5 gm. of tissue using a detergent extraction procedure. The DNA was hydrolyzed in trifluoroacetic acid and the resultant bases separated by two-dimensional paper chromatography. The amount of thymine present was determined by optical density measurements. The amount of bromouracil was determined by the amount of radioactivity in the bromouracil spot. From these data the per cent replacement of thymine by bromouracil was calculated.

The results are tabulated in Table III. In the patient, B. S. in whom BUdR was identified, 0.145 micromoles of BUdR per gram of tissue represented 4.9 per cent thymidine replacement. In this patient, rapid regression of neoplasm was noted as well as the striking depapillation of the infused half of the tongue (Fig. 1*B*). The neoplasm recurred within 2 months and a subsequent radium implantation failed to control its progress. The patient died with persistent tumor. If one assumes that the micromoles of BUdR per gram of tissue represent thymidine replacement as was

proven for B. S., then several pertinent observations are possible. For example, in patient A. C., 0.084 micrograms BUdR per gram of tissue was recovered after the initial BUdR (20 mg. over 8 hours) loading dose. A second loading dose of BUdR was administered following 5-fluorodeoxyuridine (FUdR). The FUdR was added in order to enhance the BUdR uptake. The total uptake increased to 0.129 micrograms BUdR per gram of tissue, 0.045 micrograms more than noted after the administration of BUdR alone. The net increase in incorporation, however, was less than the initial incorporation of BUdR without FUdR. In patient P. C., a relative decrease in the uptake of BUdR was noted as the patient progressed through the course of therapy. In patient E. S., multiple biopsies were analyzed in order to determine the homogeneity of uptake in the tumor. The values ranged from 0.028 to 0.045. This variation probably reflects inhomogeneities within the vascular bed of the neoplasm. In one patient (L. L.) there was 0.037 micrograms BUdR per gram of mucosa, whereas 3 biopsies from the adjacent neoplasm showed an average of 0.124 micrograms of BUdR per gram, suggesting that the neoplasm incorporated at least twice as much BUdR as the normal mucosa. The limited incorporation of BUdR in the mucosa, however, may have reflected only the large amount of fibrosis which is seen histologically rather than true epithelial incorporation.

In 2 patients, the actual bromine concentration in the tumor was determined by neutron activation analysis and the values were substantially higher than obtained by the tracer technique in other tumors. The activation analysis, however, was performed on raw tissue and the value for bromine represents bromine not only present in the DNA but also present in intra- and extra-cellular fluid compartments. We are now preparing specimens of DNA extracted from the neoplastic and normal tissue for activation analysis.

Although autoradiograms were prepared in each patient, detection of incorporation by this method was uniformly unsuccessful even after many weeks of exposure.

BLOOD BROMIDE LEVELS

Weekly determinations of the serum bromide were performed in all patients. The results were so variable that a clear relationship between BUdR dosage and serum bromide levels was not demonstrated. In some patients, the level rose to between 20 and 32 mg. per cent by about the twelfth day of the infusion and seemed to plateau. In 1 patient, a maximum of 48 mg. per cent was noted. Clinical evidence of toxicity was difficult to assess. In 3 patients, a definite daytime somnolence was observed, however, in each instance the patients were in the midst of distressing mucosal reactions which interfered with their nutrition and their normal sleep cycle and required the administration of anodynes. In several patients, serial electroencephalograms were characterized by diffuse slow wave activity which occurred after the BUdR administration.

TUMOR CONTROL

Although early regression of the neoplasm was observed, the intense mucosal reaction tended to interfere with the planned therapy to the extent that irradiation of the neoplasm might have been compromised. The clinical status of the patients is presented in Table IV. It is impossible to detect a significant difference in survival between the control and experimental groups.

DISCUSSION AND CONCLUSIONS

In the patients who received intra-arterial BUdR, early reaction in both the neoplasm and the mucosa was consistent with the results of combined radiation and BUdR treatment reported by Fletcher *et al.*[10] Contrary to their experience, we were able to demonstrate 4.9 per cent thymidine replacement by BUdR in the DNA extracted from infused neoplastic tissue in 1 instance. Early tumor response was some-

Table IV

RESULTS OF LINEAR ACCELERATOR IRRADIATION OF PATIENTS WITH ADVANCED HEAD AND NECK CANCER WITH AND WITHOUT INTRA-ARTERIAL CHEMICAL INFUSION

	X-ray Alone (9 pt.)			BUdR and MTX-BUdR (12 pt.)		
			Total			Total
Interval Since Treatment Began (mo.)	less than 12	12–24		less than 12	12–24	
Alive without Disease	1*	4	5	4		4
Alive with Disease		1	1	5		5
Dead with Disease		3	3		3	3

* Recurrence excised.

times evident along with increased cutaneous reaction, as observed by Calabresi[3] in patients receiving intravenous IUdR plus irradiation.

Clinically, useful radiosensitization with a pyrimidine analogue appears to depend upon (1) the achievement of preferential uptake of the BUdR into the DNA of the neoplastic cells, and (2) incorporation of the analogue into all of the cells of the neoplasm. Reliance upon a supposed difference in mitotic activities between normal and neoplastic tissue for achieving a differential uptake appears inadequate. In fact, the relative rates of cellular proliferation between normal and neoplastic tissue are not clearly defined. Mendelsohn,[19,20] for example, has shown that a substantial proportion of cells in murine mammary tumors are not proliferating rapidly. In normal mucosa, proliferation of the cells of the basal layer may be more orderly and occur at a more rapid rate than cells of the neoplastic counterpart. This relationship might favor analogue incorporation into normal epithelium, accounting for the intense mucosal reactions observed in this series.

Woodman[23] has recently reported achieving a favorable differential uptake of iodine in neoplastic versus normal tissues exposed to IUdR which has been complexed with the polycation, polyethylene imine. He suggests that if tumor cells have a higher anionic surface charge or the duration of the hyperanionic state is longer, then polycation complexing of the analogues might permit a preferential absorption of the pyrimidine radiosensitizers into neoplastic cells.

Suit[22] has pointed out that the ultimate radiosensitivity of a sensitized neoplasm is largely determined by that fraction of cells which does not incorporate the radiosensitizers. Methods of achieving incorporation which rely solely upon semi-conservative DNA synthesis in the normal course of cell division may never achieve sensitization of all of the cells. Other routes for the introduction of pyrimidine analogues into the DNA of neoplastic cells such as incorporation during repair of DNA injury or the use of polycation complexes as mentioned above should be investigated.

Thus despite the clinical evidence for radiosensitization of neoplastic and normal tissues alike noted in this small series, a method for achievement of differential radiosensitization of carcinoma in man with the pyrimidine analogues remains elusive.

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RADIATION DOSE FRACTIONATION AND HIGH PRESSURE OXYGEN IN RADIOTHERAPY OF THE DBA MOUSE MAMMARY CARCINOMA*

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AS A part of our preparation to investigate the place of high pressure oxygen in clinical radiotherapy, we are studying its place in radiotherapy of certain tumors of laboratory mice. Earlier investigation of the response of the mammary carcinoma of the C_3H mouse to x-radiation administered as a single dose showed that respiration of pure oxygen at 4 atmospheres of pressure absolute sharply modified tumor cure probability for small tumors (*e.g.*, less than 1 mm. in diameter), but was only slightly effective for large tumors, *e.g.*, 8 mm. in diameter which were characterized by presence of grossly necrotic areas. However, when the total radiation dose was fractionated into 10 equal doses and one dose was applied at daily intervals, even oxygen at 3 atmospheres of pressure was found to be highly effective in modifying the efficacy of irradiation of the large tumors.[2,3] The present report describes similar, but expanded studies based on the DBA mouse mammary carcinoma.

MATERIALS AND METHODS

EXPERIMENTAL ANIMAL TUMOR SYSTEM

Weanling male and female hybrid mice ($C_{57} \times$ DBA)F_1 hybrids were supplied by the Texas Inbred Mouse Company, Houston, Texas. These animals would presumably not carry the mammary tumor agent. From the same source, an adult female mouse of the DBA strain (mammary tumor agent positive) that carried a single spontaneous mammary carcinoma was obtained. Experiments described in this report are based on 2nd to 4th generation transplants derived from the single mammary carcinoma of the DBA mouse carried in these F_1 hybrid mice. The recipient mice were 8–12 weeks old at time of transplantation. Details have been previously described of: preparation of cell suspension, tumor cell transplantation, measurement of tumor volume, scoring recurrences, statistical analysis of local control results, local tumor irradiation[1,4] and of the special high pressure chambers.[2]

EXPERIMENTAL GROUPS

Groups of 125–200 sequentially numbered animals were placed by means of a random number system into one of 4 to 7 dose groups in each of the 3 dose response curve studies for either the single dose or fractionated dose radiation schedule; the randomization was performed on the day following tumor transplantation. In these experiments a total of 489 animals was used. For transplantation, an inoculum containing $2–5.10^4$ viable tumor cells was injected into the muscle mass of the right thigh. A tumor transplant take-rate of 96.5 per cent was obtained. These DBA mouse mammary carcinomas were characterized by the presence of gross necrotic and hemorrhagic areas when they were of the volume used in these studies. As the tumor size approached a mean diameter of 8 mm., the 3 diameters of the tumor were measured daily in order that treatment be started on the day that the tumor achieved the volume of interest. Thus there was a minimum

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TABLE I

DBA MOUSE MAMMARY CARCINOMA 8 MM. DIAMETER TUMOR TREATED BY SINGLE DOSE X-IRRADIATION

(Pooled Results of Triplicate Experiments)

Condition of Treatment	TCD_{50}/100 Days	95 Per Cent Confidence Limits
Anoxia	5,120	4,997....5,245
Air	4,722	4,501....4,955
O_2 30 psi	4,912	4,371....5,520

Ratios of TCD_{50}/100 Day Values

$$\frac{\text{Anoxia}}{\text{Air}} = 1.08 \qquad \frac{\text{Anoxia}}{O_2\ 30\ \text{psi}} = 1.04 \qquad \frac{\text{Air}}{O_2\ 30\ \text{psi}} = 0.96$$

variation in tumor volume at the start of treatment. All irradiations were carried out on tumors of a mean diameter of 8 mm. or a volume of $\approx$ 250 $mm.^3$. For the fractionated irradiation, treatments were applied at 24 hour ($\pm$ 1 hour) intervals or at twice weekly intervals. Radiation was administered by a pair of parallel opposed 250 kv. peak x-ray beams of 2.75 cm. diameter. Doses are expressed as dose in rads to the central position of the tumor.

RESULTS

Results of treatment of such tumors by single or fractionated doses of x-radiation are listed in Tables I through IV, and are illustrated in Figures 1 and 2. The radiation was administered under one of three conditions of local tissue oxygenation: (1) "anoxia": a heavy brass clamp was fitted across the root of the thigh for 2 minutes prior to and then during local irradiation; (2) "air": no known interference in the blood flow to the tumor bearing part; and (3) "O_2 30 psi": animal was placed in a special high pressure chamber and respired 100 per cent oxygen at 30 pounds per square inch (3 atmospheres pressure absolute) for 15 minutes prior to and then during local tumor irradiation. Table 1 shows the results of a single dose irradiation. There was a small, but significant, difference in the TCD_{50}/100 day between the anoxia and the air group. TCD_{50}/100

TABLE II

DBA MOUSE MAMMARY CARCINOMA 8 MM. DIAMETER TUMOR TREATED BY 10 EQUAL DOSES OF X-RADIATION, ADMINISTERED AT 24 HOUR INTERVALS

Condition of Treatment	TCD_{50}/100 Days	95 Per Cent Confidence Limits
Anoxia	10,950	10,039....11,944
Air	7,414	6,492.... 8,467
O_2 30 psi	6,241	4,788.... 8,136

Ratios of TCD_{50}/100 Day Values

$$\frac{\text{Anoxia}}{\text{Air}} = 1.47 \qquad \frac{\text{Anoxia}}{O_2\ 30\ \text{psi}} = 1.77 \qquad \frac{\text{Air}}{O_2\ 30\ \text{psi}} = 1.19$$

TABLE III

DBA MOUSE MAMMARY CARCINOMA 8 MM. DIAMETER TUMOR TREATED BY 10 EQUAL DOSES OF X-RADIATION, ADMINISTERED TWICE WEEKLY

Condition of Treatment	TCD_{50}/50 Days	95 Per Cent Confidence Limits
Anoxia	15,070	14,350....15,826
Air	9,896	8,508....11,511
O_2 30 psi	5,513	4,575.... 6,642

Ratios of TCD_{50}/50 Day Values

$$\frac{\text{Anoxia}}{\text{Air}} = 1.53 \qquad \frac{\text{Anoxia}}{O_2\ 30\ \text{psi}} = 2.74 \qquad \frac{\text{Air}}{O_2\ 30\ \text{psi}} = 1.79$$

TABLE IV

TIME OF APPEARANCE OF RECURRENCE: RADIATION ADMINISTERED IN 10 EQUAL DOSES AT TWICE WEEKLY INTERVALS (ANOXIC CONDITIONS AT TREATMENT)

Radiation Dose (rads)	No. Recurrence No. Treated	Times of Appearance of Recurrence (days after treatment started)
10,050	6/6	31, 34, 34, 36, 44, 49
11,930	5/5	34, 43, 44, 45, 50
15,070	6/6	44, 49, 49, 55, 88, 91
18,410	4/4	69, 69, 74, 80

day is the tumor dose which yields a local control of tumor in 50 per cent of the animals for 100 days. However, TCD_{50} for "O_2 30 psi" did not differ significantly from either the anoxia, or the air group. Thus, in this animal tumor system, the effectiveness of single doses of radiation administered to 8 mm. diameter tumors was essentially independent of the local conditions of treatment. That is, under normal or "air" conditions, the TCD_{50} values indicated that nearly all of the tumor cells were moderately to severely hypoxic. This is evidenced by the ratio TCD_{50} anoxia/TCD_{50} air of 1.08. Further, respiration of oxygen at 30 psi did not appreciably affect the tumor response. Note the similarity of the dose response curves in Figure 1, for the 3 conditions of irradiation.

Results of similar studies are shown in

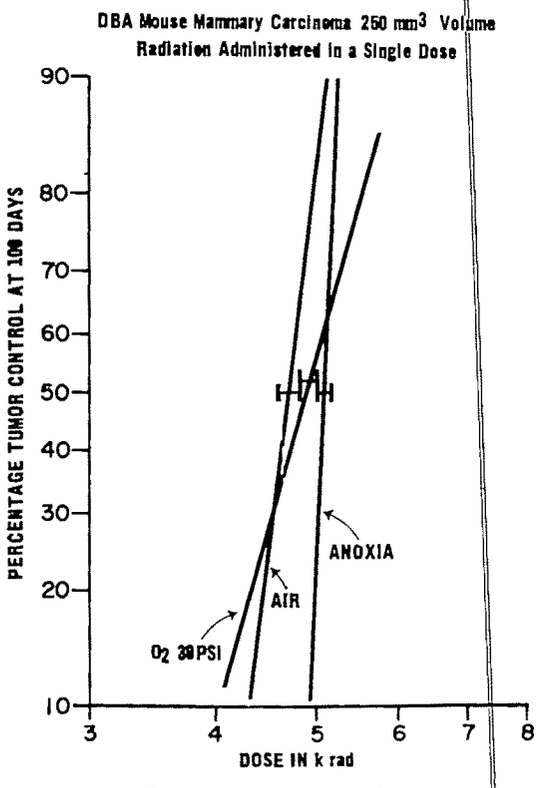


FIG. 1. Radiation dose-tumor control response curve for the DBA mouse mammary carcinoma (250 mm.^{3} volume) at 100 days after treatment by single doses of x-radiation. The brackets indicate the standard error of the TCD_{50} estimates.

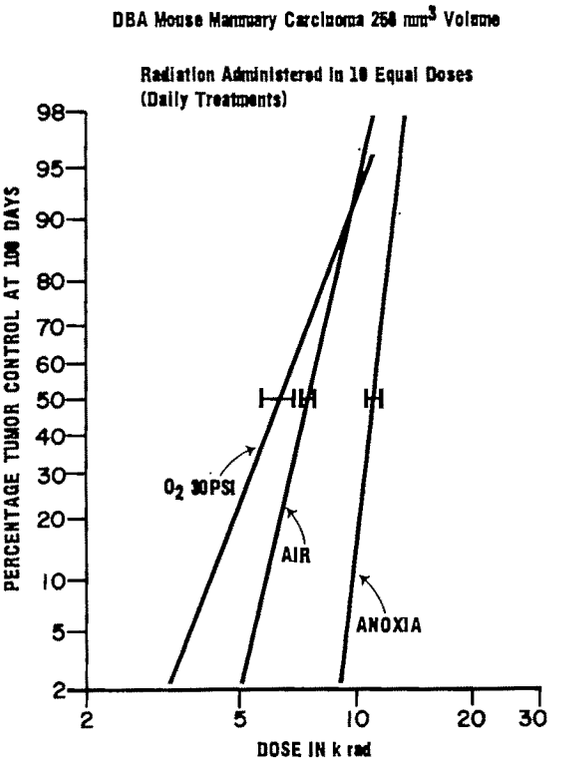


FIG. 2. Radiation dose-tumor control response curve for the DBA mouse mammary carcinoma (250 mm.^{3} volume) at 100 days after fractionated doses of x-radiation (10 equal doses, daily treatments).

Table II, except that here the radiation was administered in 10 equal doses and treatments were applied at daily intervals. In these experiments, there was a wide separation in the TCD_{50} for the anoxia and air groups, and the ratio TCD_{50} anoxia/air was 1.47, instead of 1.08 for the single dose study. Additionally, there was a wide separation in the TCD_{50} anoxia and O_2 30 psi values. The ratio was 1.77; however, the confidence limits around this particular TCD_{50} O_2 30 psi estimate were relatively wide.

In an attempt to evaluate the effectiveness of fractionated irradiation when the time intervals between treatments were greater than 24 hours, doses were administered twice a week for a total of 10 equal doses. This represents a preliminary investigation of the relationship between tumor cure probability and protraction of

dose. Note in the results given in Table III that the TCD_{50} values for anoxia, air, and O_2 30 psi group are cleanly separated from one another as shown by the 95 per cent confidence limits. The TCD_{50} ratios

$$\frac{\text{Anoxia}}{\text{Air}} \text{ and } \frac{\text{Anoxia}}{O_2\ 30\ \text{psi}}$$

were 1.53 and 2.74, respectively.

These values approach the maximum that could be expected by the use of high pressure oxygen *i.e.*, 2.5 to 3.0.

In one respect, this one set of experiments was disappointing, because all tumors eventually recurred; accordingly, we were not able to compute the TCD_{50} at more than 70 days. The observed recurrences following the very high doses employed in this assay were almost certainly due to the time available for proliferation of viable cells during the relatively long inter-treatment interval. The tumor volume doubling time was 2 days, which suggests that the mean cell generation time was ≤ 2 days. This striking influence of an inter-treatment interval, which was long in relation to the volume doubling time, is evident by inspection of Table IV. For example, 4 of the 4 tumors that received 18,410 rads (anoric) recurred between the 69th and 80th day. Although we could not estimate the TCD_{50} for times greater than 60 days, it was clearly well in excess of the 15,070 rads for 60 days.

At the unusually high doses applied, normal tissue reaction was quite severe. Unfortunately, assessment of the reaction was complicated in every instance by recurrence of tumor.

DISCUSSION

The TCD_{50}/160–180 days for the mouse mammary carcinoma of the DBA mouse when treated at the same tumor volume by single dose irradiation under anoxic conditions was the same as that for the mammary carcinoma of the C_3H mouse. The TCD_{50} values were: 5,676 rads [5,465 . . . 5,894] and 5,756 rads [5,559 . . . 5,961] for the DBA and the C_3H tumors respectively; the figures in brackets represent the 95 per cent confidence limits around the TCD_{50} estimate. This is of interest not only because the tumor originated in different strains of mice, but also because of differences in tumor growth rates: the DBA tumor was very rapidly growing (volume doubling time of 2 days) and the C_3H tumor grew less rapidly (volume doubling time of 4 days). Also, the two tumor systems were similar in that treatment under "air" or "O_2 30 psi" conditions was much more effective as compared with treatment under "anoxia" for fractionated than for single dose irradiation. A plausible explanation for this greater effectiveness of fractionated therapy could be that during fractionated therapy and the accompanying regression of tumor volume, there is an increase in tumor tissue pO_2 and a more marked rise in pO_2 when the animal respired O_2 30 psi. This might be the result of a decrease in intercapillary distances with tumor regression. Van Putten and Kallman[5] have studied a sarcoma in the C_3H mouse and interpret their data as showing an increased tissue pO_2 during fractionated therapy. The greatly enhanced oxygen effect factor for protracted and fractionated therapy (twice weekly treatments) raises the question as to what extent the "therapeutic ratio" might be improved by proper selection of protraction and fractionation factors in the treatment of very slowly growing tumors. In an effort to determine how typical is the effect of dose fractionation to enhance the oxygen effect factor for tumor tissue, we have further experiments in progress which are based on a fibrosarcoma and a squamous cell carcinoma of the C_3H mouse.

SUMMARY

Radiobiological studies of the DBA mouse mammary carcinoma have shown that for single dose irradiation of 8 mm. diameter tumors the response is essentially the same for irradiations given under

anoxia, air, O_2 30 psi conditions. If, however, the irradiations are administered at 10 equal doses at 24 hour intervals, the ratio TCD_{50} anoxia/TCD_{50} O_2 30 psi is 1.77, instead of approximately 1.08 for the single dose irradiation. This is further increased to approximately 2.7, when the radiation is administered at twice weekly instead of daily intervals. These results suggest that the effectiveness of high pressure oxygen in improving results of radiation therapy may be highly dependent on the dose fractionation schedule employed.

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HYBAROXIC RADIATION THERAPY*

REVIEW OF TWO YEAR EXPERIENCE WITH 167 PATIENTS

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DURING the past 14 years, an increasing body of evidence has accumulated to affirm the relationship between radiation sensitivity of a cell and its oxygen tension. This phenomenon has been demonstrated in various plant and animal systems and has been coined the "oxygen factor."

The principle was applied to radiation therapy in 1954 by Churchill-Davidson,[6,7] in London. van den Brenk has reported the largest clinical series as well as much of the radiobiologic work.[14–18] Excellent discussion of the subject and review of the literature were published by Wildermuth [20,21] and Wootton.[26]

At a recent Symposium on Hyperbaric Radiation Therapy, the experience with over 1,500 patients was reported from 6 different therapy centers throughout the world.[4,5,10,11,19,22] (Table 1). Churchill-Davidson,[5] van den Brenk,[19] and Johnson[10] have tried to match some cases treated with hyperbaric oxygen with like cases treated in air, some with similar and some with different techniques. Unfortunately, no truly randomized series has been reported to this point, although this is being attempted in England with bronchogenic carcinoma,[9] in New York by Chang[4] with glioblastoma multiforme and carcinoma of the tonsil and by us[11] with bronchogenic carcinoma and bladder tumors at this time.

Regardless of how impressive the results with individual lesions at various sites may be as compared to other techniques, the whole answer to the question of the advantage of hyperbaric irradiation over irradiation at atmospheric pressure cannot be given satisfactorily until such randomized series with comparable treatment techniques have been completed.

The basis of clinical radiation therapy with high pressure oxygen is well depicted in Figure 1, *A*, *B* and *C*, devised by Wildermuth[23] after a concept by Scott,[12] and histologic studies by Thomlinson and Gray.[13] Figure 1*A* shows the tumor cells growing around a capillary. If tumor cells continue to grow beyond a distance of 200 micra from a capillary, frank necrosis will develop. Between 150 and 200 micra distance, cells will be progressively anoxic but still viable. If we administer what we consider to be an adequate tumor dose, we may kill most of the tumor cells which are reasonably well oxygenated, but still find

Table I

NUMBER OF PATIENTS TREATED WITH HPO_2 MEGAVOLTAGE REPORTED NOVEMBER, 1965, SAN FRANCISCO, CALIFORNIA

1. van den Brenk[18]	Melbourne, Australia	614
2. Wildermuth[22]	Seattle, Washington	460
3. Churchill-Davidson[5]	London, England	235
4. Plenk and Card[11]	Salt Lake City, Utah	153
5. Johnson[10]	Winnipeg, Manitoba, Canada	25
6. Chang[4]	New York, New York	23
		1,510

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
From the Tumor Institute, St. Mark's Hospital, Salt Lake City, Utah.

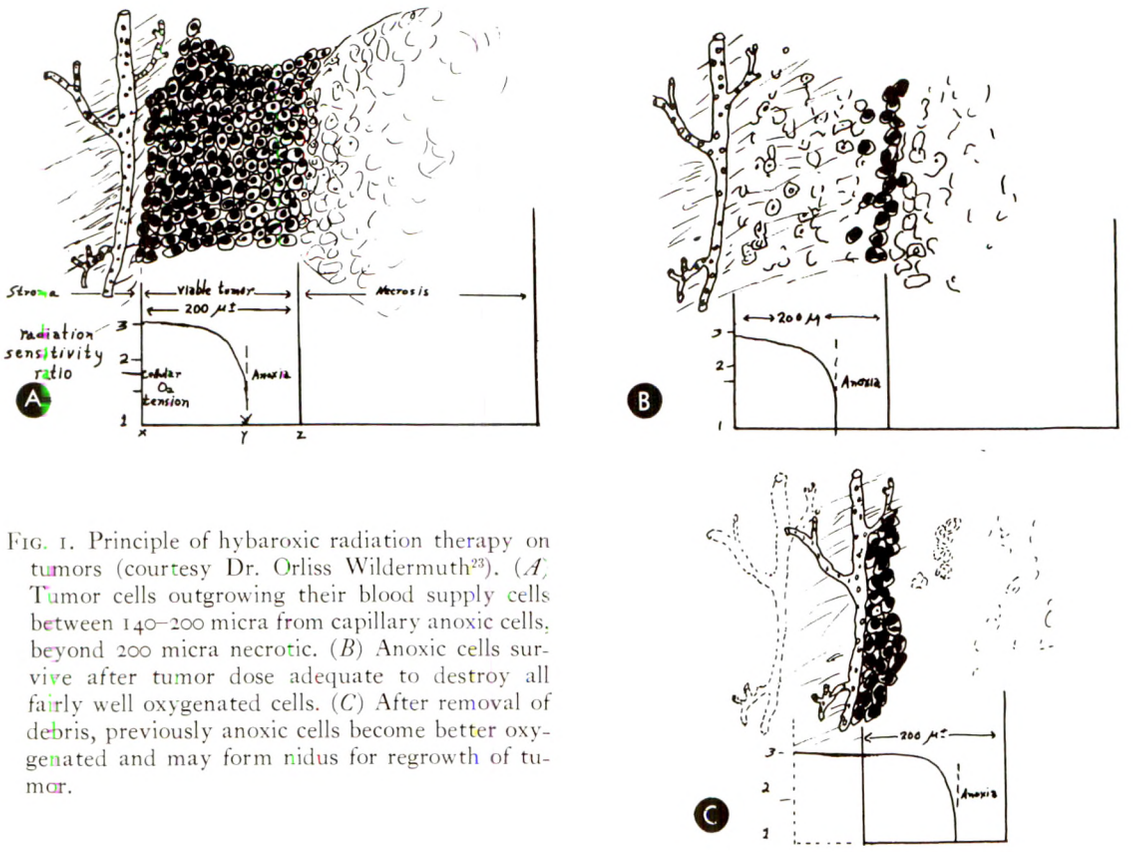


FIG. 1. Principle of hybaroxic radiation therapy on tumors (courtesy Dr. Orliss Wildermuth[23]). (*A*) Tumor cells outgrowing their blood supply cells between 140–200 micra from capillary anoxic cells, beyond 200 micra necrotic. (*B*) Anoxic cells survive after tumor dose adequate to destroy all fairly well oxygenated cells. (*C*) After removal of debris, previously anoxic cells become better oxygenated and may form nidus for regrowth of tumor.

that some of the anoxic cells will survive (Fig. 1*B*). These cells may serve as a nucleus for regrowth of tumor, especially when their blood supply is improved, after removal of debris from destroyed cells (Fig. 1*C*). If we can oxygenate all cells optimally, smaller doses of radiation will have a more uniform lethal effect on all tumor cells. The most effective way to increase oxygen tension of tissues is through breathing oxygen under 3 or 4 atmospheres or pressure.

We began using a Vickers Hyperbaric Chamber on February 15, 1964 and our experience during the first 2 years of operation is here reported. The distribution of lesions treated is shown in Table II. We completed therapy on 167 patients by February 15, 1966, discarding 12 other patients whose treatment had to be discontinued for various reasons (Table III). In 2 additional patients, treatment was discontinued because of a desired change in the modality of treatment.

TECHNIQUE

The patient is placed on the stretcher of the hyperbaric chamber. The chamber is sealed and the air is flushed out by a stream of oxygen. The pressure is gradually increased to 30 pounds per square inch gauge pressure (45 pounds absolute) in approximately 10 to 15 minutes for the average patient. A 5 minute "soaking period" is used before moving the chamber into the "cobalt room." The move and set-up of the field take approximately 3 minutes on the average so that the patient remains at full pressure of 3 atmospheres for a minimum of 8 minutes. This corresponds to Wootton's[24] recommendation of 7 minutes and 15 seconds for optimal oxygenation. The average treatment time is between 8 and 15 minutes to produce a

daily tumor dose of 400 to 600 r. Decompression is started immediately as the timer of the cobalt 60 machine clicks off and while the patient is still in the cobalt room. This takes an additional 5 to 7 minutes. The average time for the patient in the chamber is between 35 and 50 minutes.

Relatively few patients are unable to tolerate this procedure, mostly because of claustrophobia. In our own experience, 8 patients (5 per cent) refused to go back into the chamber after the first treatment.

We found that patients with previous neck dissection frequently have difficulty in clearing their ears and we had to discontinue treating 1 patient for this reason. Three additional patients with previous neck dissections have tolerated the high pressure well following myringotomy.

All of our patients were conscious and cooperative. We have never used anesthesia. Nose drops, antihistamines and ear drops (Auralgan) were used frequently, tranquilizers rarely.

We began with total tumor doses be-

TABLE II

TUMOR INSTITUTE ST. MARK'S HOSPITAL HYPERBARIC OXYGEN CHAMBER PATIENTS

(February 15, 1964 through February 15, 1966)

Area		Total	Living	Expired
Lip (lost to follow-up)		1	1 (Presumed)	
Tongue, Tonsil, Mouth		22	12	10
Tongue	10		2	8
Tonsil	4		4	
Floor of Mouth	3		3	
Soft Palate	3		2	1
Epiglottis	2		1	1
Ear		1		1
Sinuses		3	3	
Mandible		1	1	
Brain*		8	5	3
Primary	5		4	1
Metastatic	3		1	2
Cervical Metastases		2		2
Pharynx		4	3	1
Hypopharynx	2		2	
Nasopharynx	1			1
Oropharynx	1		1	
Larynx		7	3	4
Intrinsic	6		3	3
Extrinsic	1			1
Thymoma		1	1	
Thyroid		1		1
Glomus Jugulare		1		1
Esophagus		10	4	6
Lung*		51	15	36
Primary	42		10	32
Metastatic	9		5	4
Stomach		3		3
Anus		1		1
Pancreas		2		2
Gallbladder		1		1
Liver		1		1
Kidney		1		1
Ureter		1		1
Adrenal		1	1	
Bladder	13	13	7	6
Prostate		5	3	2
Female Reproductive Organs		10	2	8
Cervix	7		1	6
Vulva	1			1
Endometrium	2		1	1
Miscellaneous		1		1
Sarcoma		3		3
Metastatic Areas		3		3
Retreatments		8	4	4
Total		167	65	102
Distontinued Treatment		12		
Total		179		
* Patients treated for lung and brain tumors		2		

TABLE III

USE OF CHAMBER DISCONTINUED

1. Fear, claustrophobia	8
2. Inability to clear ears due to previous neck dissection	1
3. Pneumothorax following therapy with chamber	1
4. Violent nausea and vomiting after coming out of chamber	1
5. Chamber out of order	1
Total	12

tween 3,200 and 3,500 r in about 35 days, based somewhat on Wildermuth's experience, at the time we started. This was given in 10 treatments of 3-4-3 treatments each on alternate days, with 1 week of rest between each course of 3 or 4 treatments. When we observed a number of recurrences in patients whose lesions responded well initially, we gradually increased our average dose to 10 times 400 r and finally to 12 times 400 r tumor dose in 3 courses of treatments on alternate days with approximately 1 week rest period between each course of 4. This gave us a tumor dose of 4,800 r administered in a period of approximately $5\frac{1}{2}$ to 6 weeks.

Since the first annual San Francisco Cancer Symposium in November of 1965 when Churchill-Davidson[3] and van den Brenk[19] reported higher rates of local tumor control than we had experienced, we have used Churchill-Davidson's technique of 6 times 600 r tumor dose in approximately 17 or 18 days, especially in the head and neck area. This dose schedule seemed to result in somewhat more dramatic tumor response but did increase over our previous technique the local radiation reaction, especially mucositis in the mouth.

In the past, our complication rate was very low. Whether or not the more rapid dose schedule will increase our complication rates remains to be seen. This is probably justified if corresponding improvement in survivals and tumor control can be demonstrated.

COMPLICATIONS

We have experienced 13 incidents (Table IV) which can be attributed to barotrauma. Most of these were changes in the appearance of the eardrum with more or less definite evidence of hemorrhage on the inner aspect of the drum on inspection. Three additional patients discharged serosanguineous fluid from the nose and one from the ear.

In 5 patients, dry to moist epidermitis was of the magnitude of that seen with comparable doses of 250 kv. radiation therapy. Mild epidermitis is not unusual and is brought about by the scattering of radiation by the plastic tank which absorbs about 16 to 17 per cent of the radiation, depending upon the size of the field. The distance from the patient to the inside of the tank wall is not quite enough for complete absorption of all of the photoelectrons produced by the scattering from the plastic shell.[25] Because of the long collimator of the Picker C 5,000 cobalt 60 unit, it is necessary to raise the patient in the chamber so that the distance between the inner wall of the chamber and the skin is between 12 and 13 cm. Otherwise, the distance of 80 cm. cannot be maintained and the field set-up is somewhat more complicated.

One of our worst complications was a severe slough of the abdominal wall, roughly corresponding to the treatment field in a very obese patient. This patient will be alluded to later.

The most serious life threatening incident was a pneumothorax in 1 patient with carcinoma of the lung who had moderate

TABLE IV

COMPLICATIONS OF HYPERBARIC OXYGEN CHAMBER PATIENTS

1. Injuries to Ear Drum	9
Drum hemorrhage	
Serosanguineous fluid:	
Nose	3
Ear	1
2. Epidermitis, severe	5
3. Slough of Abdominal Wall	1
4. Pneumothorax	1
5. Vesicovaginal Fistula	$1\frac{1}{2}$
6. Perforation (bladder)	1
7. Perforation (ileum)	1
8. Small Bowel Fistula	1
9. Radiation myelitis?	
Unilateral foot drop	1
Bilateral vague neurologic changes	1
10. Gastrostomy	
Obstruction of pharynx	1
11. Nausea and Vomiting after Coming out of Chamber	2
12. Vomiting in Chamber	1
13. Myringotomy	3

pulmonary emphysema. He required rapid decompression and emergency measures because of vascular collapse and cyanosis. Neurologic changes in 2 patients have to be ascribed to early radiation myelitis. Some of the remaining complications may have occurred as a result of the disease itself, but 2 later complications, a small bowel fistula and a perforation of the ileum occurring 1 year after successful radiation therapy, need to be noted. We have not observed any seizures which can be attributed to oxygen.

METASTASES

We have encountered rather unusual metastases, some of which may have been accelerated by the oxygen therapy. In 2 patients with head and neck lesions, metastases to the lung became apparent or were much more striking before completion of the course of therapy, although the initial chest roentgenogram was negative in 1 patient and only slightly suggestive of disease in another patient. One patient with bronchogenic adenocarcinoma, who had a negative bone survey at the onset of therapy, developed a pathologic fracture of the femur with an extensive destructive lesion not quite 2 months later.

We found liver metastases in a patient with a tumor of the false cords which may or may not be significant. In 1 patient (Case IV) with a crater-like lesion on the undersurface of the tongue, massive cervical metastases within and outside of the treatment field developed rather promptly.

It would be difficult to be certain that any of these patients developed these metastases because of the oxygen therapy since we have seen some similar rapidly growing metastases in patients who were in a control group and have not received oxygen.

Johnson[10] has reported a slight increase in distant metastases, some in unusual sites, following hyperbaric treatment of a series of 25 patients with Stage III and IV carcinoma of the cervix, treated with daily tumor doses of 200 rads to total tumor doses of 5,750 to 6,600 rads. This was compared with a matched prior series of 25 cases. The difference did not seem to be significant statistically, and the 2 groups are also not entirely comparable. The possibility that 30 exposures to hyperbaric oxygen may be more productive of such unusual metastatic growth has to be considered. We do not believe that there is sufficient evidence to conclude that unusual or more frequent metastases are a serious threat of hybaroxic therapy.

RESULTS

During the first 12 months, we tried to gain experience with all types of lesions. The distribution of these lesions is shown in Table II. During the past year, we have been more selective and also have randomized our patients with carcinoma of the lung and with carcinoma of the bladder so that some of our patients are now treated with hyperbaric techniques, while others are treated with more conventional cobalt 60 techniques in air at atmospheric pressure. Without true randomization in advance, it is certainly extremely difficult to compare treatment methods even in one's own institution. The comparison of material from one institution with that of another certainly leaves much doubt as to the validity of the data. We will try to assess the results in our 2 largest disease groups: (1) bronchogenic carcinoma, and (2) lesions of the upper respiratory and digestive passages.

BRONCHOGENIC CARCINOMA

The treatment results of bronchogenic carcinoma of various series in air and high pressure oxygen are listed in Table V. Our 1 year survival rate was 35 per cent in inoperable carcinoma with or without exploratory thoracotomy. Patients with known distant metastases beyond the mediastinal, scalene or supraclavicular lymph nodes were not treated. Similar results were reported by Churchill-Davidson[5] and van den Brenk.[19] These figures with the use of oxygen seem to be better than

TABLE V

BRONCHOGENIC CARCINOMA

Survival Statistics:	Comparison of various treatment series in air and high pressure oxygen (not randomized)		
		One Year Survival	Per Cent
Churchill-Davidson St. Thomas Hospital London, England	Air	1/19	5
Churchill-Davidson[5]	HPO_2	5/21	24
Peter McCallum Clinic Records Melbourne, Australia	Air	49/331	14
van den Brenk[18,9] Peter McCallum Clinic Melbourne, Australia	HPO_2	9/20	45
Plenk and Card Tumor Institute St. Mark's Hospital Salt Lake City, Utah	Air (all patients treated in 1962 and 1963 including those with pleural fluid and distant metastases)	14/55	25
	Air (disease confined to the mediastinum and supraclavicular area)	13/39	33
	HPO_2	12/34	35
Bloedorn *et al.*[3] University of Maryland (preoperative irradiation)	Air (all patients)	26/192	13
	Air (resectable tumor only)	19/98	23
Guttmann[9] Delafield Hospital New York, New York	Air	60/153	40

the results in patients treated in air by these 2 authors and also compare favorably with the 1 year survival in preoperatively irradiated patients by Bloedorn and others,[3] in spite of the fact that their patients were subjected to surgery and operable lesions are included. However, Guttmann's[8] unusually good results with conventional cobalt 60 therapy alone in 5,000–6,000 r doses compare very favorably with either of the oxygen series.

We were not able to improve results in our own comparable but not randomized material treated with 5,500–6,000 r cobalt 60 tumor dose without oxygen in 1962 and 1963. The difference is not significant statistically. Our randomized series has not progressed far enough for evaluation.

Figure 2 shows the breakdown in our results related to the histology of the tumor. Somewhat to our surprise, the cases of undifferentiated carcinomas actually did better than the squamous cell carcinomas.

UPPER RESPIRATORY AND DIGESTIVE PASSAGES

Churchill-Davidson[5] and van den Brenk[19] reported 46 per cent and 43 per cent 12 month survivals respectively in advanced lesions of the head and neck (Table VI). Our 1 year survival rate of 42 per cent is similar to that of the British

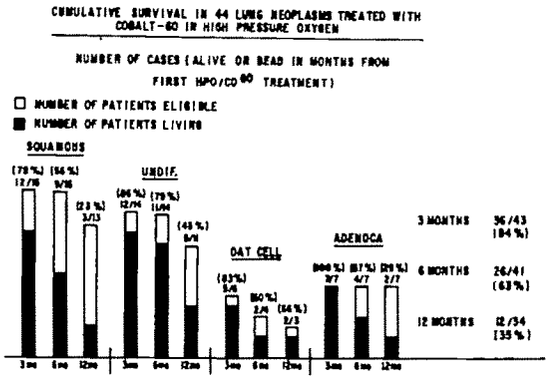


FIG. 2. Cumulative survival in 44 lung neoplasm cases treated with Co^{60} teletherapy in high pressure oxygen. Number of cases alive or dead in months from first Co^{60} HPO_2 treatment.

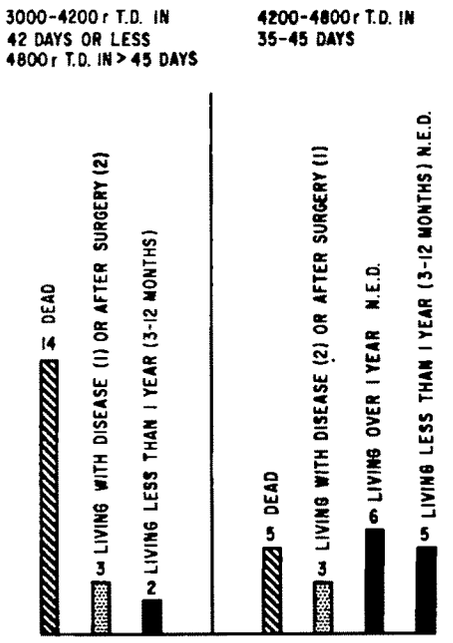


FIG. 3. Thirty-eight patients with upper respiratory and digestive tract disease, treated before Dec. 15, 1965, related to tumor dose Co^{60} HPO_2.

and Australian clinics. The rate of clearance of the primary lesion as well as of the lymph nodes is comparable. The same is true with the 6 month pessimistic clearance rate.

If we separate our patients into two groups, those who received less than 4,200 r in 25–35 days and those receiving 4,800 r in more than 45 days, and compare the results with the group receiving 4,200 to 4,800 r in 35–45 days, we find a striking difference in the results of these 2 groups (Fig. 3). While the results in the first

TABLE VI

RESPIRATORY AND UPPER DIGESTIVE PASSAGES

(Advanced Lesions)

		Primary Clearance (per cent)	Lymph Node Clearance (per cent)	Both* (6 mo. or more) (per cent)	12 mo. Survival (per cent)
Churchill-Davidson[5] St. Thomas Hospital London, England		56	73		46
van den Brenk[19] Cancer Institute Melbourne, Australia		64	70	56	43
Plenk and Card St. Mark's Hospital Salt Lake City, Utah	Entire series 38 cases	70	60	45	42
	Less than 4,200 r 19 cases	61	33	38	21
	Over 4,200 r 19 cases	91	81	77	67

* Pessimistic clearance rate: all patients dead with or without disease at 6 months are excluded.

group with lower tumor dose or greater protraction are somewhat discouraging, the results in those patients receiving mostly 4,800 r tumor dose in 35–45 days seem quite gratifying. We have included some less advanced patients during the last year which certainly has helped to improve the results.

We are now finding it difficult not to use hybaroxic therapy in even the earlier cases, since the response seems to be gratifying, the reaction less than seen with ordinary therapy and fewer implants or surgical procedures seem to be required.

The following case reports are examples of: (1) spectacular local tumor regression with long term result, histologically proven; (2) local tumor control in lung and (3) in bladder in spite of distant metastases; (4) disappointing localized recurrence in spite of initial spectacular regression; (5) similar dramatic response in one of our control cases; and (6) one of our most serious complications.

REPORT OF CASES

Case I. A 78 year old male presented with an exophytic 3×4 cm. epidermoid carcinoma of the right tonsil, extending towards the gingiva of the right mandible and the base of the tongue. The classification was $T_3N_1M_0$ (Fig. 4*A*). The patient was treated between January 19 and March 4, 1965 to a tumor dose of 4,812 r in 44 elapsed days, with cobalt 60 HPO_2, resulting in prompt remission with complete disappearance of the lesion. One week after completion of therapy, the mucosa was entirely healed and the tumor bed was restored to normal (Fig. 4*B*). About 1 month later, 3 biopsies from the tumor site did not reveal any evidence of residual tumor. A scheduled radon implantation was cancelled. The patient is alive and well 14 months later.

Case II. A 50 year old male showed a right parahilar and mediastinal mass on roentgenograms (Fig. 5*A*). Anaplastic carcinoma was identified from a scalene lymph node biopsy. Invasion of the brachial plexus was present. Treatment consisted of 4,800 r tumor dose, with cobalt 60 HPO_2 given between November 10 and December 16, 1964 in 36 elapsed days. The



Fig. 4. Case I. P.B. Exophytic carcinoma of tonsil extending into base of tongue. (*A*) Prior to cobalt 60 HPO_2 radiation therapy. (*B*) One week after completion of cobalt 60 irradiation to 4,800 r tumor dose.

tumor had practically disappeared after 3,200 r. Figure 5*B* demonstrates the appearance of the chest 8 weeks after completion of treatment.

Considerable fibrosis of the right upper lobe developed 4 months post therapy, but remained unchanged until his death 5 months later. The patient was readmitted in June, 1965 with progressive weakness, vomiting, weight loss and difficulty in walking and expired 1 week later. Postmortem examination revealed no evidence of tumor in the right chest but there was extensive tumor replacement of the pituitary, adrenals, pancreas and retroperitoneal lymph nodes.

Case III. In a 68 year old male, an inoperable anaplastic transitional cell carcinoma of the urinary bladder was found (classification Jewett: CIV). Pretherapy roentgenograms showed a large defect in the left base of the urinary

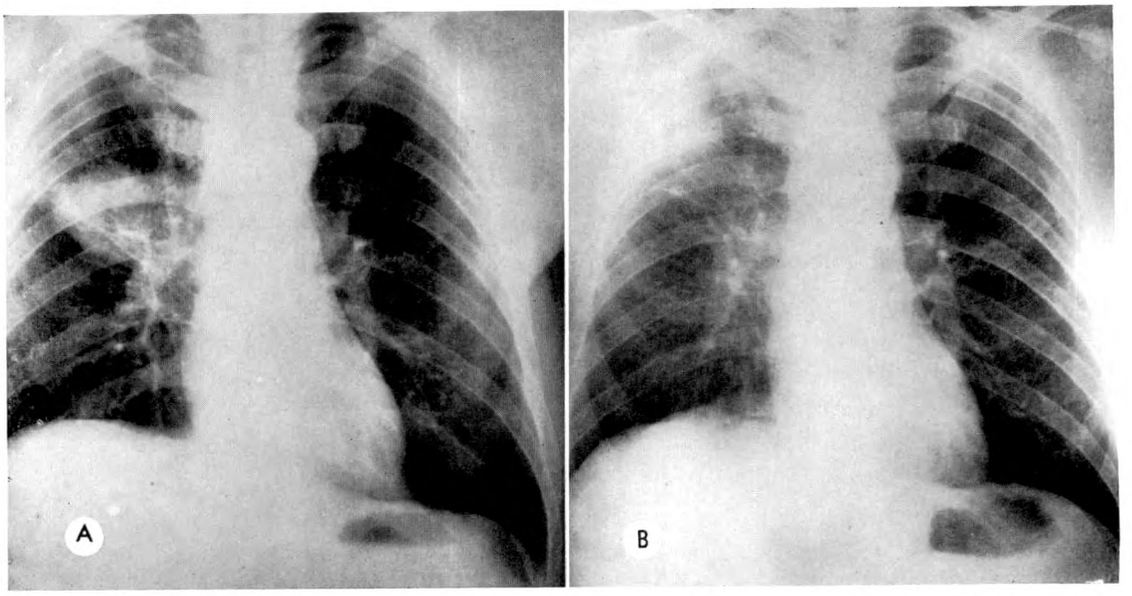


FIG. 5. Case II. N.H. (*A*) Chest roentgenogram showing anaplastic bronchogenic carcinoma in right upper lobe and right hilar lymph nodes prior to cobalt 60 HPO_2 radiation therapy. (*B*) Eight weeks after 4,800 r tumor dose with cobalt 60 HPO_2 radiation therapy.

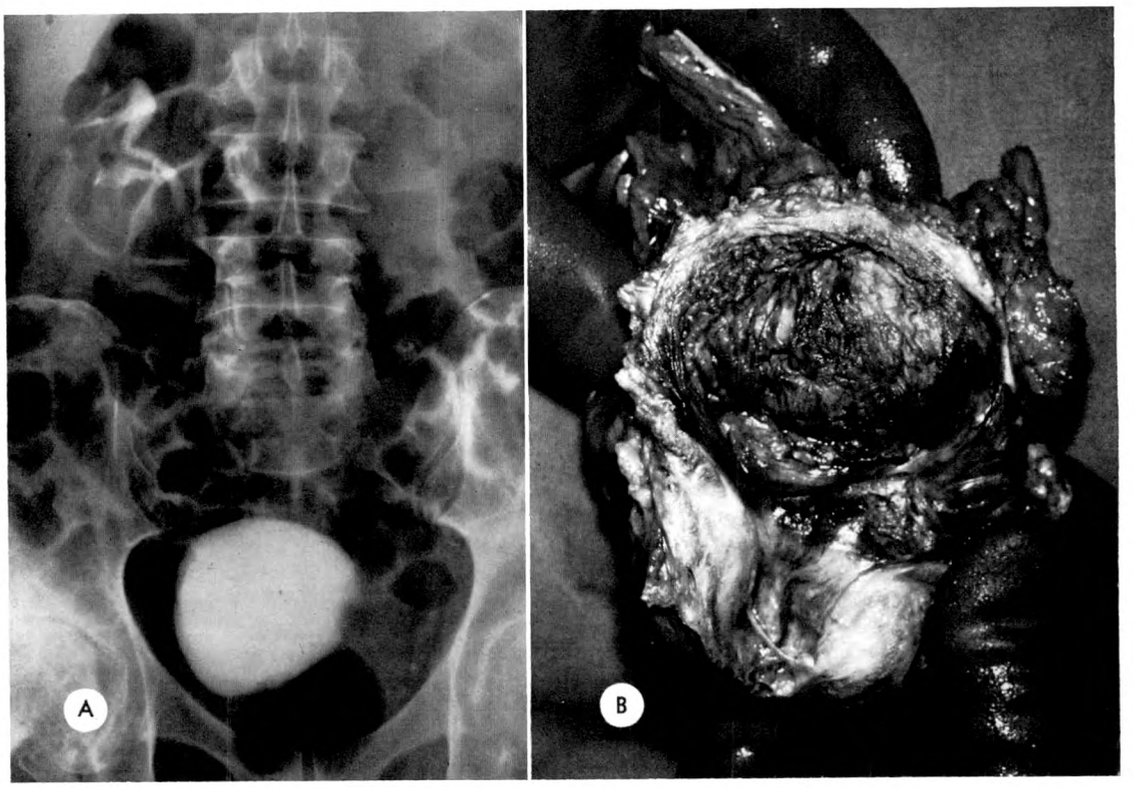


FIG. 6. Case III. O.T. (*A*) Excretory urogram shows defect in left lower pole of bladder with nonfunctioning left kidney prior to cobalt 60 HPO_2 radiation therapy to a tumor dose of 4,250 r. (*B*) Postmortem specimen of urinary bladder 9 months later is free of tumor.

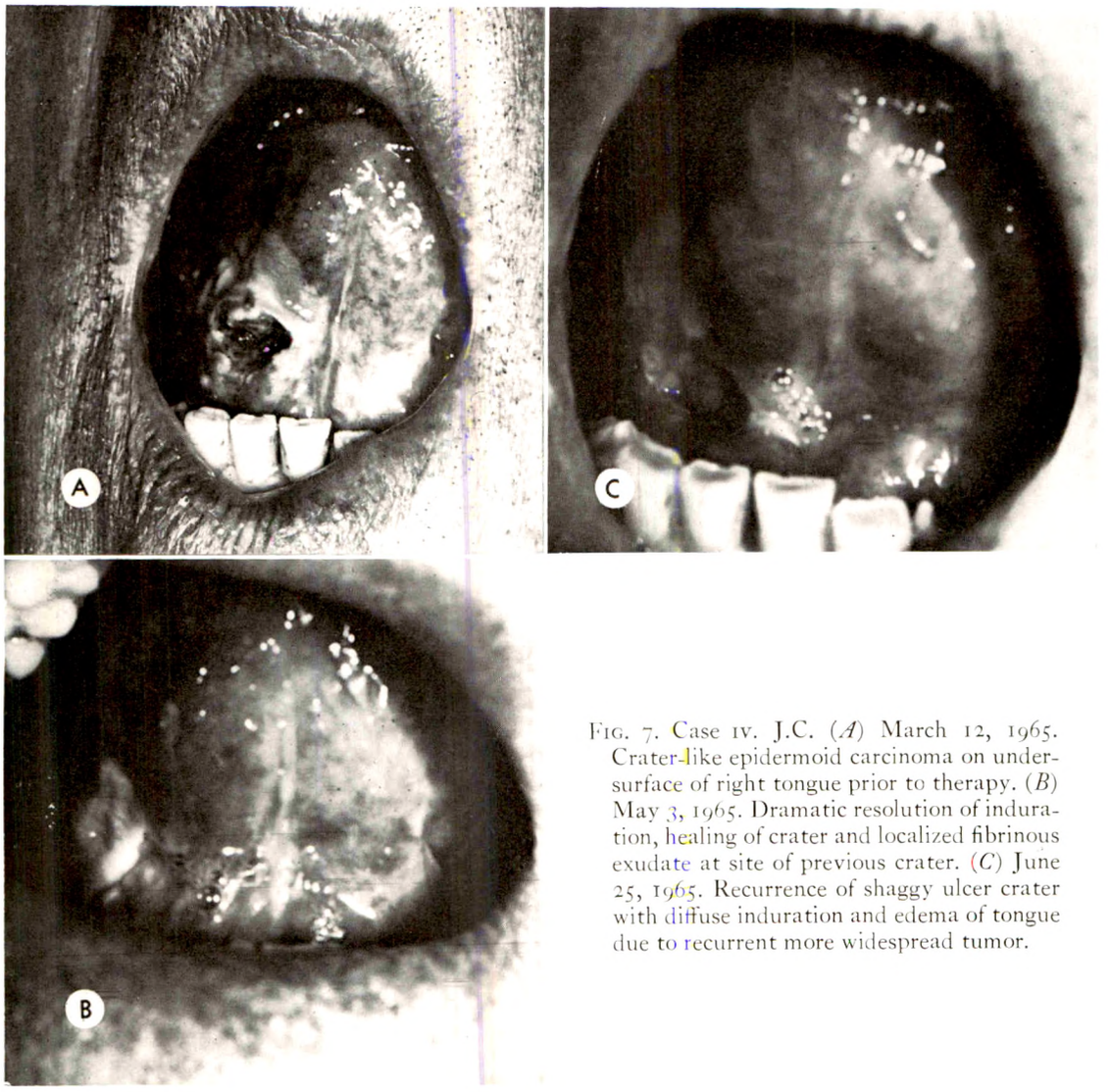


Fig. 7. Case IV. J.C. (*A*) March 12, 1965. Crater-like epidermoid carcinoma on undersurface of right tongue prior to therapy. (*B*) May 3, 1965. Dramatic resolution of induration, healing of crater and localized fibrinous exudate at site of previous crater. (*C*) June 25, 1965. Recurrence of shaggy ulcer crater with diffuse induration and edema of tongue due to recurrent more widespread tumor.

bladder with obstruction of the left ureter (Fig. 6*A*). He was treated with cobalt 60 HPO_2 to a 4,250 r tumor dose between September 17, 1964 and October 21, 1964, and excellent remission with good symptomatic relief resulted. However, in the middle of June, 1965, nine months after onset of therapy, the patient experienced loss of equilibrium, weakness, vomiting and dizziness. He went downhill rapidly and died 1 month later on July 13, 1965. Postmortem examination revealed no tumor in the bladder (Fig. 6*B*) or in the pelvis, but cerebral metastases which apparently caused his demise were observed.

Case IV. This 78 year old male was first seen on March 12, 1965 with a deeply indurated crater on the undersurface of the right side of the tongue which was diagnosed as a squamous cell carcinoma. One small supraclavicular lymph node was palpable. The classification was $T_3N_1M_0$ (Fig. 7*A*). One week after the administration of a 1,600 r tumor dose (4 times 400 r in 8 days), the exophytic portion of the lesion had disappeared and the ulcer was already partially healed. On the day of the last treatment on May 3, 1965, a tumor dose of 4,836 r with cobalt 60 HPO_2 in 52 elasped days was achieved in the depth of the tongue calculated at the midline. The lesion had practically disappeared and some fibrinous exudate covered the area of the previous ulcer crater (Fig. 7*B*). Healing progressed and no evidence of indura-

tion was seen on May 24, 1965. However, 1 month later on June 25, 1965 a deep necrotic ulcer crater with extensive angry induration of the entire anterior half of the tongue was apparent. Massive cervical lymph nodes had developed within and outside of the field of radiation (Fig. 7*C*).

The patient was not considered suitable for further surgery and died 2 months later.

This was our most dramatic case of good ini-

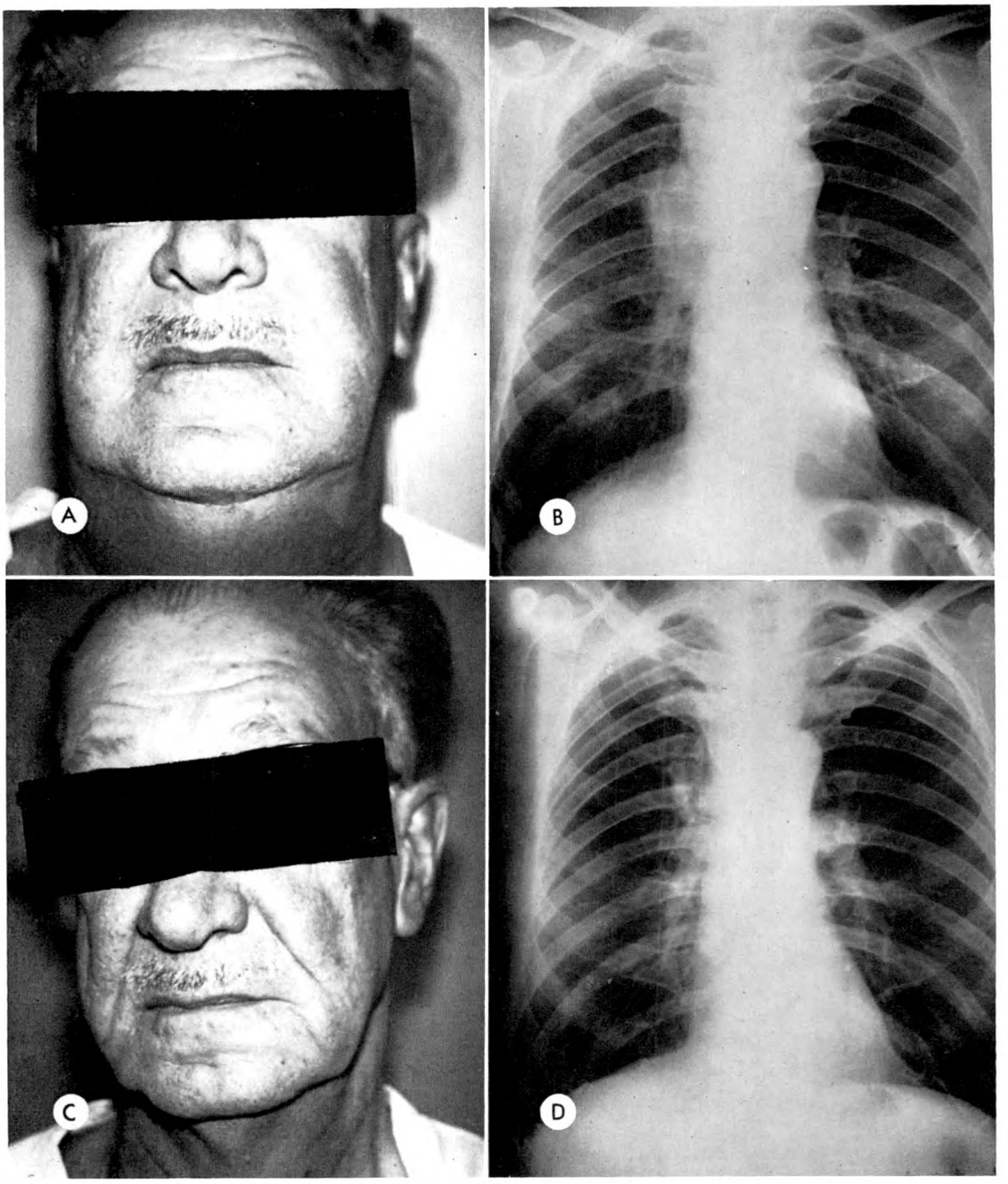


Fig. 8. Case v. V.B. (*A*) April 30, 1965. Striking swelling of face and neck due to superior vena cava obstruction. (*B*) Chest roentgenogram shows massive right hilar and paratracheal tumor mass due to anaplastic epidermoid carcinoma of bronchus. (*C*) May 7, 1965. Patient's appearance 7 days after onset of cobalt 60 radiation therapy and tumor dose of 1,183 r. (*D*) May 19, 1965. Roentgenogram of chest 7 days after tumor dose of 1,966 r. Patient did not have oxygen.

tial response with very disappointing rapid recurrence of localized tumor as well as of metastases in the regional lymph nodes. The greater than usual protraction over 52 days because of severe mucositis may play a role in the treatment failure in spite of the total tumor dose of 4,836 r.

Case v. A 65 year old male with progressive swelling of the eyelids, face and entire neck, characteristic of superior vena cava obstruction syndrome (Fig. 8*A*), had a diagnosis of anaplastic epidermoid carcinoma of the bronchus, noted on the chest roentgenogram (Fig. 8*B*), and verified by right supraclavicular lymph node biopsy. He was treated between April 30 and June 17, 1965 to a tumor dose of 5,526 r with cobalt 60 in 48 elapsed days. At the end of the first course of therapy at 1,183 r, the neck was almost normal in size (Fig. 8*C*) and a definite decrease in the hilar mass was apparent on the roentgenogram after a tumor dose of 1,966 r was delivered (Fig. 8*D*).

The progress continued in very dramatic fashion. It needs to be stressed that this patient was one of our control patients who did not receive oxygen but was treated with a similar technique of 400 r tumor dose per day on alternate days. Had this patient been treated in the chamber, we would have been impressed by the dramatic change which we would have been inclined to attribute to the oxygen effect.

Case vi. A 67 year old female with a history of subtotal hysterectomy in 1938 had vaginal bleeding for 1 year prior to 1956 when a diagnosis of carcinoma of the cervical stump was made and she was treated elsewhere with external and intravaginal roentgen-ray therapy (250 kv. peak).

The lesion disappeared and the patient was symptom free until February, 1964, when a granular reddish lesion involving the proximal one-half of the vagina, especially on the left side, was biopsied and an epidermoid carcinoma was demonstrated.

The patient was treated in the hyperbaric chamber between March 10 and April 17, 1964, when a total tumor dose of 3,312 r was achieved in the midplane at a depth of 13 cm. The vaginal lesion resolved promptly. The air dose at the anterior surface was 5,175 r, at the posterior surface 1,725 r.

In December, 1964, the patient had developed brawny induration of the anterior skin and eventual stenosis of the upper half of the vagina. Minimal ulceration of the skin was apparent on March 5, 1965. This progressed to an area of deep subcutaneous slough about 15 cm. in diameter, roughly corresponding to the treatment field by July, 1965 (Fig. 9*A*). The patient was quite disabled though her general condition remained very good and no evidence of tumor was discovered.

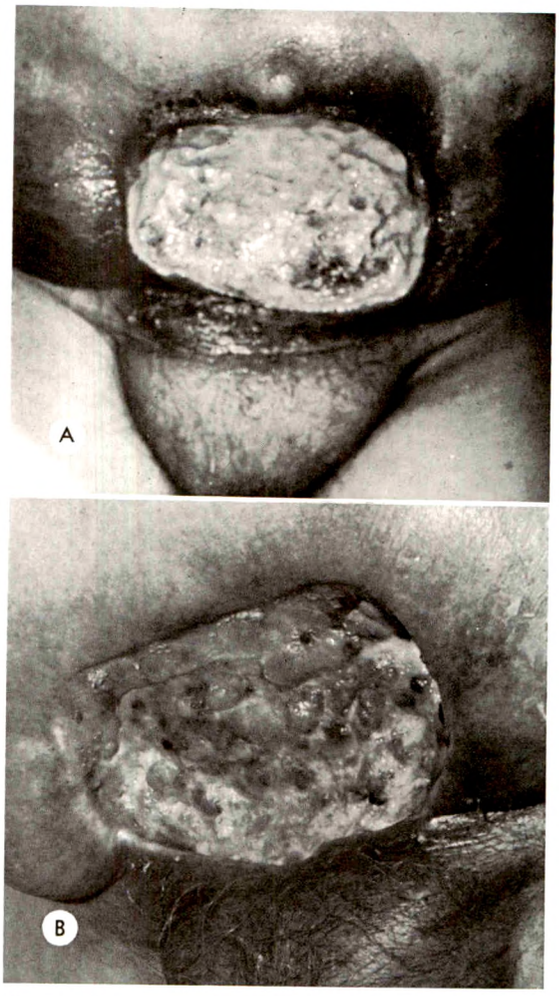


Fig. 9. Case vi. H.C. (*A*) Deep ulceration of abdominal wall 1 year after cobalt 60 HPO_2 radiation therapy for recurrent carcinoma of cervical stump. (*B*) Some healing was noted after pinch grafts.

In December, 1965, some pinch grafts were applied which took and some healing was also noted at the periphery of the ulcer (Fig. 9*B*). The patient has remained tumor free 2 years since the onset of radiation therapy, and healing of the defect is still progressing.

The unequal dose administered to the anterior and posterior surfaces was due to the patient's refusal to lie prone after 3 treatments.

This was obviously an error in technique and judgement, since the extreme obesity already required a larger than average air dose for the desired tumor dose in the midplane.

This complication emphasizes the importance of very careful dosimetry and planning when treating with HPO_2, since even normal but poorly vascularized tissues like fat or cartilage may tolerate radiation less well than in air.

DISCUSSION

We feel that hyperbaric radiation therapy with megavoltage units is a valuable method in the hands of the radiotherapist. Smaller tumor doses seem to be capable of producing more dramatic results of tumor shrinkage and control than could be expected from comparable doses of conventional megavoltage therapy. One of the difficulties, however, arises from the fact that few of us have had the experience of treating large numbers of patients with the kind of dosage schedules used by most investigators with oxygen.

Atkins and others,[1,2] van den Brenk,[19] and Chang[4] have had dramatic results from massive tumor doses in the 800 to 1,250 rad range for single treatments without oxygen. In van den Brenk's[19] experience, the results with massive dose treatment in air are not comparable with those obtained with similar dose schedule in oxygen. We likewise have seen good results with our treatment schedule of 400 r per day in lung tumors without the use of oxygen, but it is too early to come to any conclusions about the over-all results in the randomized series.

Our greatest disappointment and concern have been the persistence of tumor within the radiation field and the recurrence of some tumors after initial excellent response in head and neck lesions with our earlier techniques. We have found this less commonly with the larger treatment doses of over 4,200 r, given in 35–45 days, and hope that we will be able to increase our local tumor control rate further with our present treatment schedules.

Although Churchill-Davidson[5] claims that the complications in his patients disappeared after he reduced the dosage to 6 times 600 r, in Wildermuth's[23] initial experience with this dosage, some complications did occur.

We believe that the treatment with hyperbaric cobalt 60 radiation therapy has made unnecessary some implantations with radon or interstitial radium applications which otherwise would have been necessary.

When larger, single tumor doses are utilized, both by necessity and by choice, it becomes extremely important that very careful field positioning be employed. The slightest error in field set-ups on any one day may produce underdosage of one portion of a tumor with disastrous results. The dangers to normal tissues from this type of dosage, especially to the spinal cord and the bowel, have to be stressed. Oxygen does not protect normal tissues; in fact, it may make even normal tissues, especially cartilage and fat, somewhat more susceptible to the effects of radiation.

Until large series of randomized material can be evaluated, the use of hyperbaric oxygen remains an investigative method.

SUMMARY

1. In a 2 year period, 167 patients were treated with cobalt 60 radiation therapy while inhaling 100 per cent oxygen at 3 atmospheres of pressure. No patient was anesthetized. Results in cases of head and neck lesions and bronchogenic carcinoma are reported.

2. Hybaroxic radiation therapy seems to produce more dramatic tumor regression than conventional dose techniques and probably also than comparable higher individual tumor dose techniques without oxygen.

3. Few interstitial implantations are required with hybaroxic therapy in head and neck lesions.

4. Head and neck lesions seem to respond particularly well to oxygen. While we were underdosing tumors initially, our present results are very gratifying. Local

recurrences seen mostly with earlier smaller doses were reduced with present techniques.

5. No significant number of undue complications or of unusual metastases was observed.

6. Time-dose schedules become very critical, and very accurate field set-up at *each* treatment is crucial since the slightest error even once can result in underdosing the tumor.*

7. In bronchogenic carcinoma, our results compare quite favorably with those of other published series but hybaroxic oxygen radiation therapy has not produced any significant improvement over earlier therapy in a nonrandomized group in our own material.

8. It is still essential to carry out randomized studies to evaluate the effect of oxygen in the treatment of tumors at various sites.

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* Our most common present technique consists of 4 treatments of 400 r tumor dose on alternate days with 5 days rest period to a total of 4,800 r tumor dose in approximately 5 weeks.

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Vol. 99, No. 4

PHYSICAL ASPECTS OF HIGH ENERGY ELECTRON THERAPY*

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IT IS a real privilege to participate in this symposium on the "Advantages and Disadvantages of Electron Beam Therapy," particularly with the authorities in its therapeutic application assembled here. I should like to outline some of the fundamental and unique properties of high energy electrons which are pertinent to their therapeutic application as well as discuss treatment planning procedures with illustrations of such applications. For these illustrations I am indebted to the cooperation of Dr. Ralph Phillips and the other members of our Department of Radiation Therapy.

High energy electrons may be defined as those with a penetration of at least 2 cm. in tissue which applies to electrons with energies of 6 MeV or greater. It is appropriate at this point to pay tribute to the foresight of Professor Donald W. Kerst of the University of Illinois who carried out the primary development of the betatron and who planned for its biologic and clinical application. It was Professor Kerst who interested Dr. Henry Quastler, Radiologist at the Carle Clinic, in the applications of the betatron and made him a member of the Physics Department. Both Professor Kerst and Dr. Quastler focused the attention of some of our staff on biologic and clinical applications.

High energy electron therapy with patients commenced in 1950 at the University of Illinois College of Medicine.[1,6,7] Although we had been able to carry out pertinent physical experiments prior to initiation of therapy, most of the treatment planning procedures were developed concurrently with therapeutic use and extended on from 1950. The actual procedures, including the system for correction of inhomogeneities, have already been summarized in the literature[10,12,13,16] and cannot in the available time be described in detail.

Before illustrating some actual plans and procedures I should like to emphasize a few of the important and unique properties of high energy electrons. Just as their nature is fundamentally different from that of x-rays, their absorption is entirely different. With high energy electrons we deal with an initially monochromatic spectrum, whereas the spectrum of x-rays is continuous. X-rays are absorbed exponentially, which is gradually, with always a portion transmitted and with consequently an appreciable exit dose. Electrons, however, lose energy almost uniformly with depth leaving essentially no dose beyond any specified depth, and certainly no appreciable exit dose.

Although the cavity ionization chamber is probably still the most convenient detector which is reliable for dosimetry, it requires calibration as a function of energy, primarily due to the polarization phenomenon. This is illustrated in Figure 1 which shows a depth dose distribution as measured absolutely in rads by the calorimetric method[14] and the apparent dose distribution as measured by a cavity ionization chamber with stopping power corrections. It is apparent that a correction factor which varies with energy and depth is required.

An indication of the reliability of the calorimetric method is indicated in Table 1 which is taken from an article by Bradshaw[2] in last year's issue of "Physics in Medicine and Biology." It is apparent that the calorimetric method as used in

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Part of the Symposium: The Advantages and Disadvantages of Electron Beam Therapy.
From Memorial Hospital for Cancer and Allied Diseases, New York, New York.

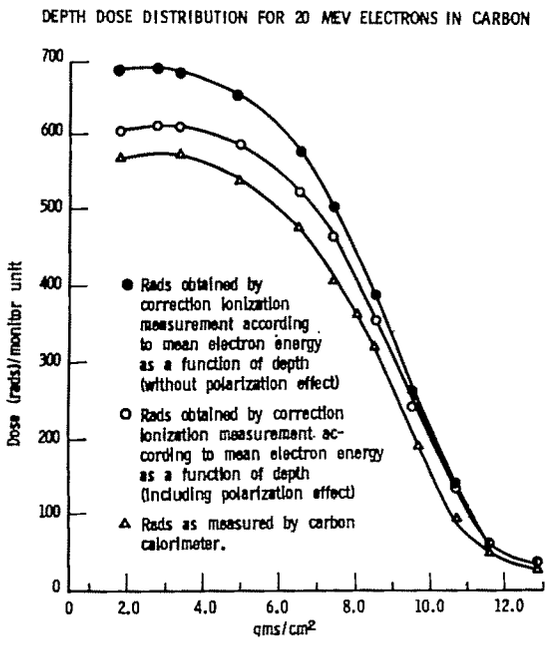


FIG. 1. Electron beam depth dose determined by calorimeter and by corrected ionization chamber measurements. (Courtesy of Proceedings of the XIth International Congress of Radiology.[14])

TABLE I

COMPARISON OF RESULTS AT 15 MEV WITH OTHER PUBLISHED DATA FOR 10 AND 20 MEV ELECTRONS (Bradshaw[2])

Nominal Electron Energy (MeV)	Rads in Carbon per "250 KV R" 1.25 cm. deep in polystyrene	Author
10	0.743±0.019	Geisselsoder *et al.*[4]
20	0.740±0.012	Geisselsoder *et al.*[4]
15	0.742±0.014	Bradshaw[2]

two different laboratories has led to the same results in terms of rads per ionization unit.

The unique central axis depth dose pattern characteristic of electrons can be theoretically derived. In Figure 2 is shown a theoretically derived dose distribution

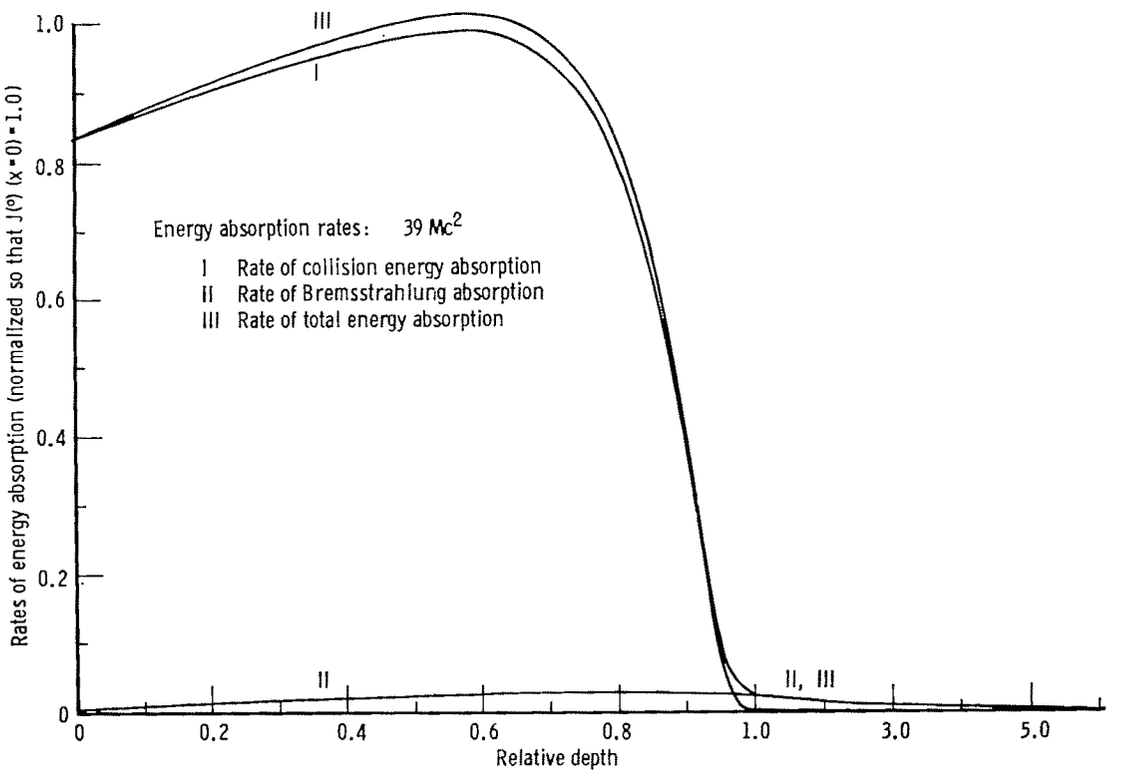


FIG. 2. Calculated electron beam depth dose distribution. (Courtesy of N. Kessaris and *Radiation Research.*[5])

due to Kessaris,[8,9] who has solved the transport equation for electrons by the moment method. The lower curve refers to the dose produced in water by the absorption of the x-rays produced in water by the absorption of the electrons. Measurements have indicated that this dose up to 24 MeV for large fields is approximately 2 per cent of the maximum dose.

Although the incident electrons have a monoenergetic spectrum, this spectrum becomes somewhat degraded with depth in the patient. This has been examined in an extensive series of measurements by Harder[5] in Germany and by Epp *et al.*[3] at Sloan-Kettering Institute. The plot in Figure 3 illustrates the flux of electrons in an indicated energy interval plotted against energy as measured by Dr. Epp. Since correction factors for ionization chambers are strongly dependent upon energy, such spectral detail is essential.

A practical result of theoretic calculations is the plot shown in Figure 4 which gives the calculated ratio of absorbed dose

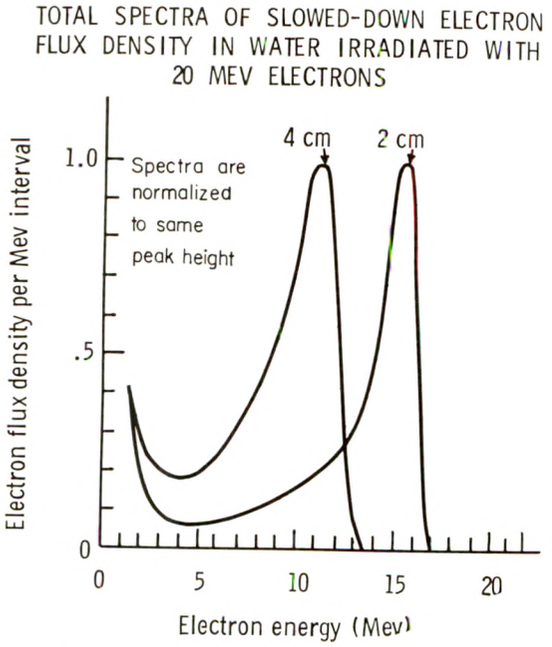


FIG. 3. Measured total electron spectra at indicated depths inside tissue equivalent material irradiated by 20 MeV electrons. (Courtesy of E. R. Epp, *et al.*[3] and the Proceedings of the XIth International Congress of Radiology.)

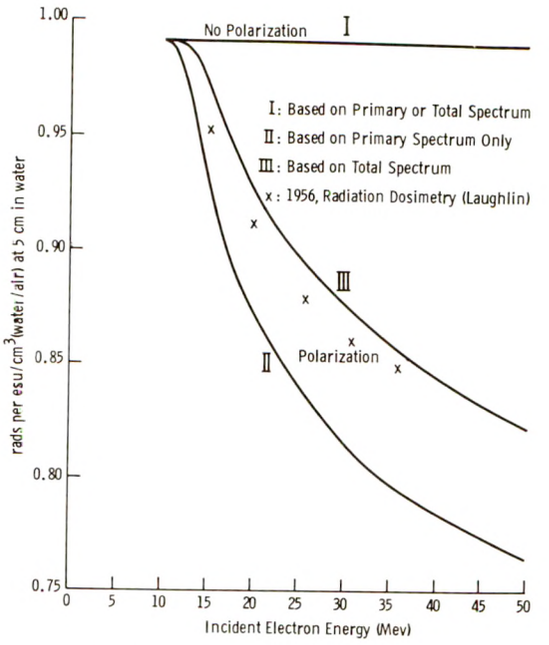


FIG. 4. Calculated ratio of absorbed dose per unit cavity ionization at a depth of 5 cm. in water irradiated by electrons with the indicated incident energies. Curve I indicates no energy dependence in this ratio if the polarization phenomenon is ignored. Curve II shows the ratios obtained with the use of the primary measured spectra shown in Figure 3. Curve III shows the calculated ratios when the spectra in Figure 3 are employed with also a secondary spectrum below 1 MeV assumed to increase inversely with energy. The curve denoted by the plotted X's is based on proportions of primary and secondary electrons obtained from cloud chamber observations.[11]

in rads per cavity ionization chamber measurement. Although this is a calculated curve, measurements have confirmed its validity.

For calibration the oxidation of the ferrous ion in ferrous sulfate solution has proved to be a convenient absorbed dose dosimeter and reliable when used with care. Intercomparisons with the ferrous sulfate dosimeter, as well as with cavity ionization chambers, have been carried on for many years between institutions using high energy electrons.[15,18] In particular, intercomparisons between the Memorial Hospital, Gustav Roussy Institute, and the M. D. Anderson Hospital, have indicated a continuing uniformity and consistency in

TABLE II

ELECTRON BEAM THERAPY AT MEMORIAL HOSPITAL
(through 1965)
NUMBER OF PATIENTS AND NUMBER OF PLANS
(in parentheses)

Head and Neck	Breast Cancer	Other	Total
782 (1,379)	647 (1,078)	188 (265)	1,617 (2,723)

calibration over a period of years. Such intercomparisons were earlier carried out on the occasion of personal visits with the carrying of an instrument. Starting in 1964 it was possible to develop methods for mailing sealed dosimeter solutions for intercomparison purposes.[17]

A sub-committee appointed by the American Association of Physicists in Medicine has produced a protocol[19] outlining recommended procedures for the measurement of absorbed dose with high energy electrons and has recommended the Fricke ferrous sulfate dosimeter as the most convenient method of choice. In their protocol all of the necessary parameters including the material and size of the phantom are specified.

Since the first use of electrons at Memorial Hospital,[11] a major objective has been to achieve realism in treatment planning. This has required extensive construction of several phantoms of different sizes of tissue-equivalent material with incorporated skeletons, air passages, and simulated lungs. Studies have been carried out with these phantoms as well as with more simple arrangements of materials representing fat, muscle, air, lung, and bone to determine the effect of body inhomogeneities on the distribution of electron dose. Also, a treatment planning system was developed which allowed the systematic correction for presence of inhomogeneities. Comprehensive planning of cases with correction for inhomogeneities is con-

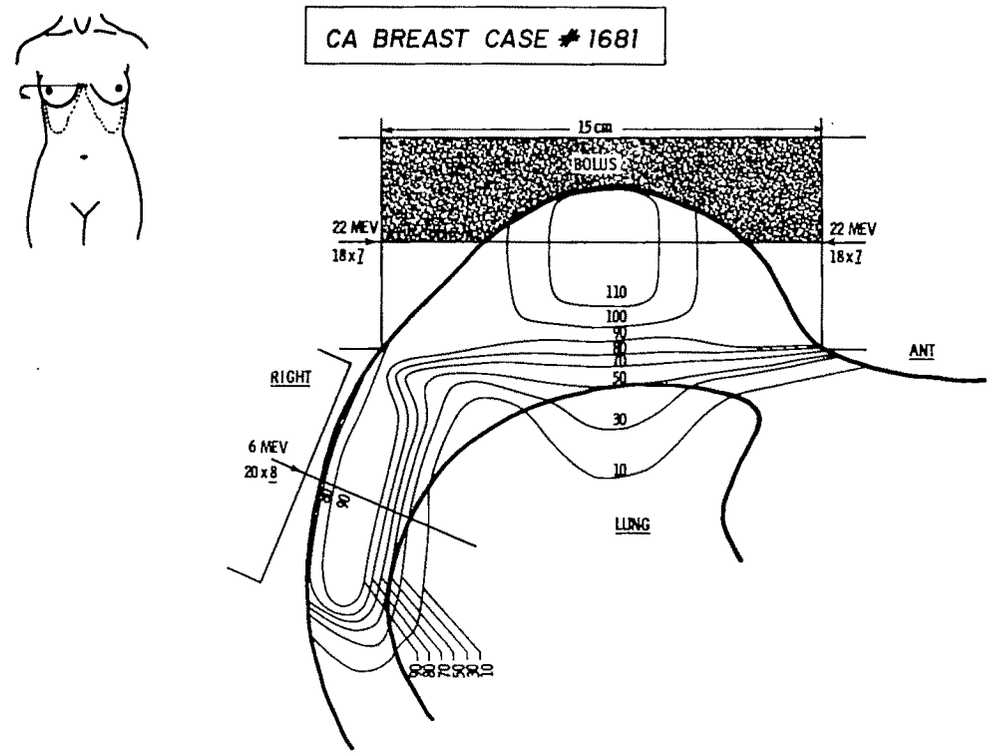


FIG. 5. Treatment plan for breast cancer resulting from Hodgkin's disease illustrating the use of tangential electron fields with bolus material.

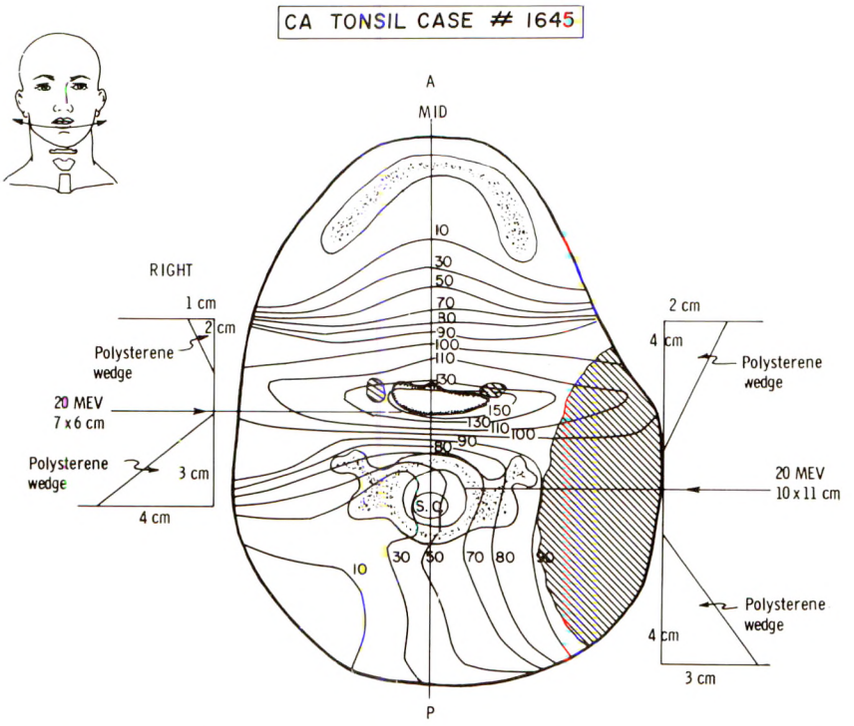


Fig. 6. Treatment plan for epidermoid carcinoma of both tonsils. As in other cases, the effects of surface curvature and inhomogeneous tissue structure, specifically of air and bone regions, have been incorporated.

sidered essential and has been carried out over the past decade primarily for lesions associated with breast cancer and in the head and neck region. The limitation on such planning has been the availability of anatomic detail.

A few representative treatment plans will be illustrated. Table II presents statistics of the numbers of cases treated up through 1965 at Memorial Hospital in the site categories of head and neck, and breast cancer, as well as others. Over 1,600 patients have been treated and approximately 2,700 treatment plans have been designed in connection with their treatment. A treatment plan for a breast cancer resulting from Hodgkin's disease is shown in Figure 5. The plan illustrates the use of bolus material with the electron beam as well as an axillary field in order to include both the breast and infiltration noted in the posterolateral aspects of the right chest wall.

The case shown in Figure 6 is an epidermoid carcinoma of both tonsils. The patient had a mass about 10 cm. in diameter in the left neck near the tail of the parotid gland which extended into the inframastoid area and involved the posterior triangle. Because of the asymmetry of the primary lesions and the large left neck mass it was elected to treat him with electrons.

The treatment plan in Figure 7 illustrates the treatment of a chest area in a case of metastatic adenocarcinoma in the dermis. When using large fields which are necessarily directed at an acute angle with respect to each other there is always the possibility of a "hot spot," particularly with x-rays. In this case it should be noted that the use of a wedge together with the limited range of these electrons makes it possible to deliver this kind of treatment without any appreciable hot spot.

The plan in Figure 8 shows the treatment of metastases in the medial third of the left clavicle. These metastases were secondary to kidney cancer. The enhanced

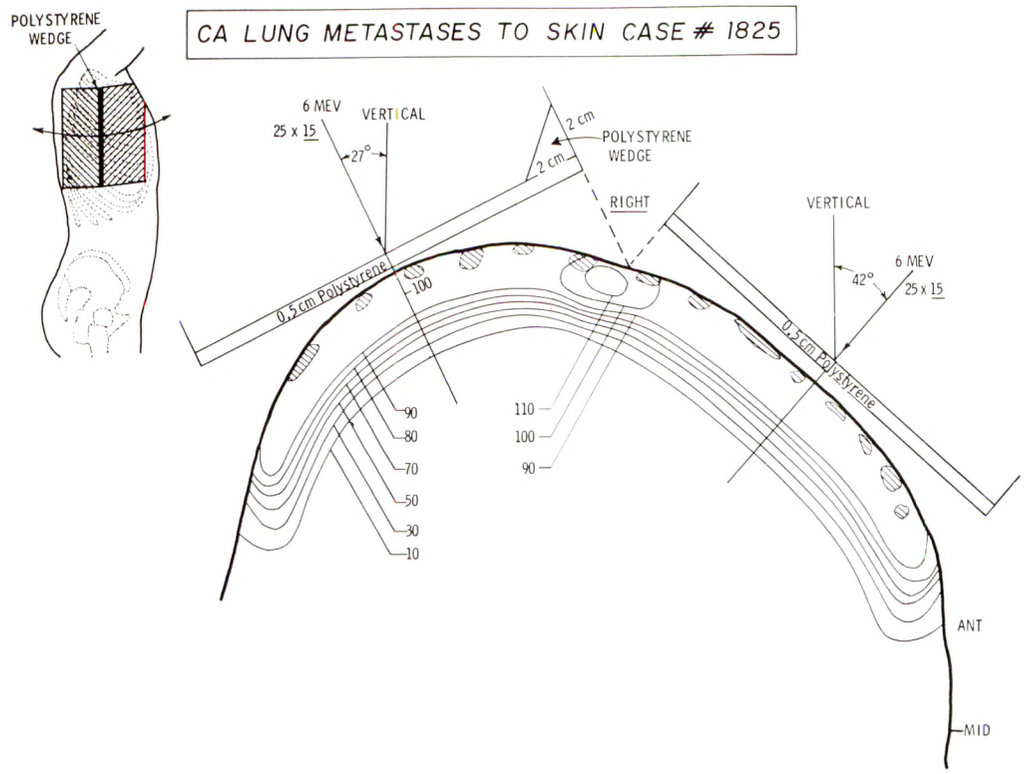


FIG. 7. Treatment plan for chest area for metastatic adenocarcinoma. A wedge is employed to avoid excessive accumulation of dose in overlapping field area.

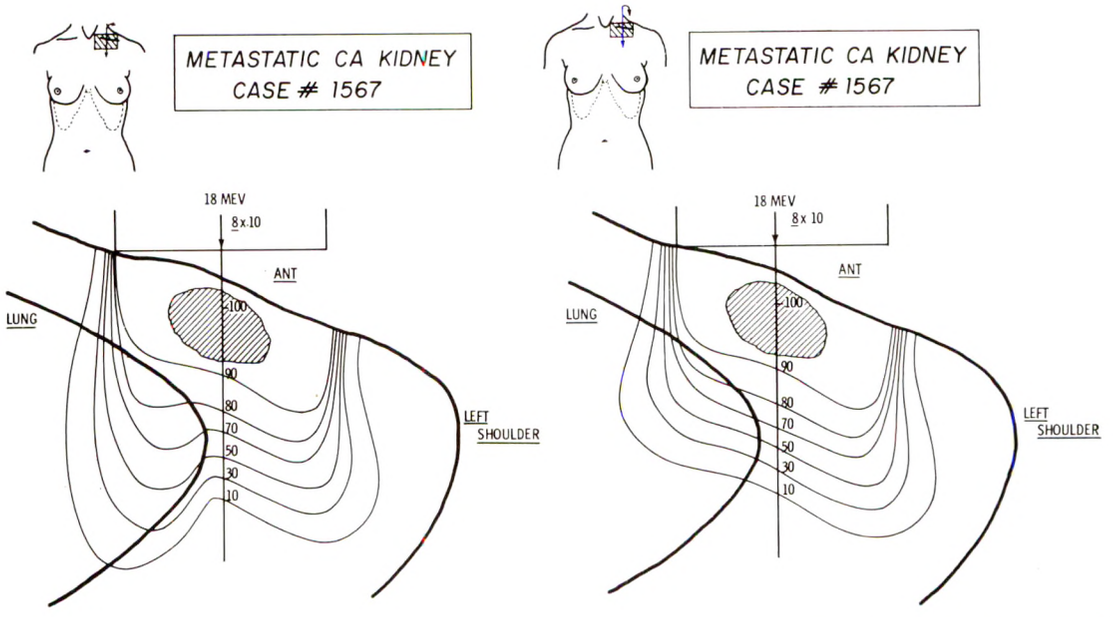


FIG. 8. Correction for presence of inhomogeneous structure is routinely incorporated when the internal anatomy is known. The plan on the left shows the higher exposure, although judged acceptable, that the lung tissue actually receives in the treatment of metastases secondary to kidney cancer.

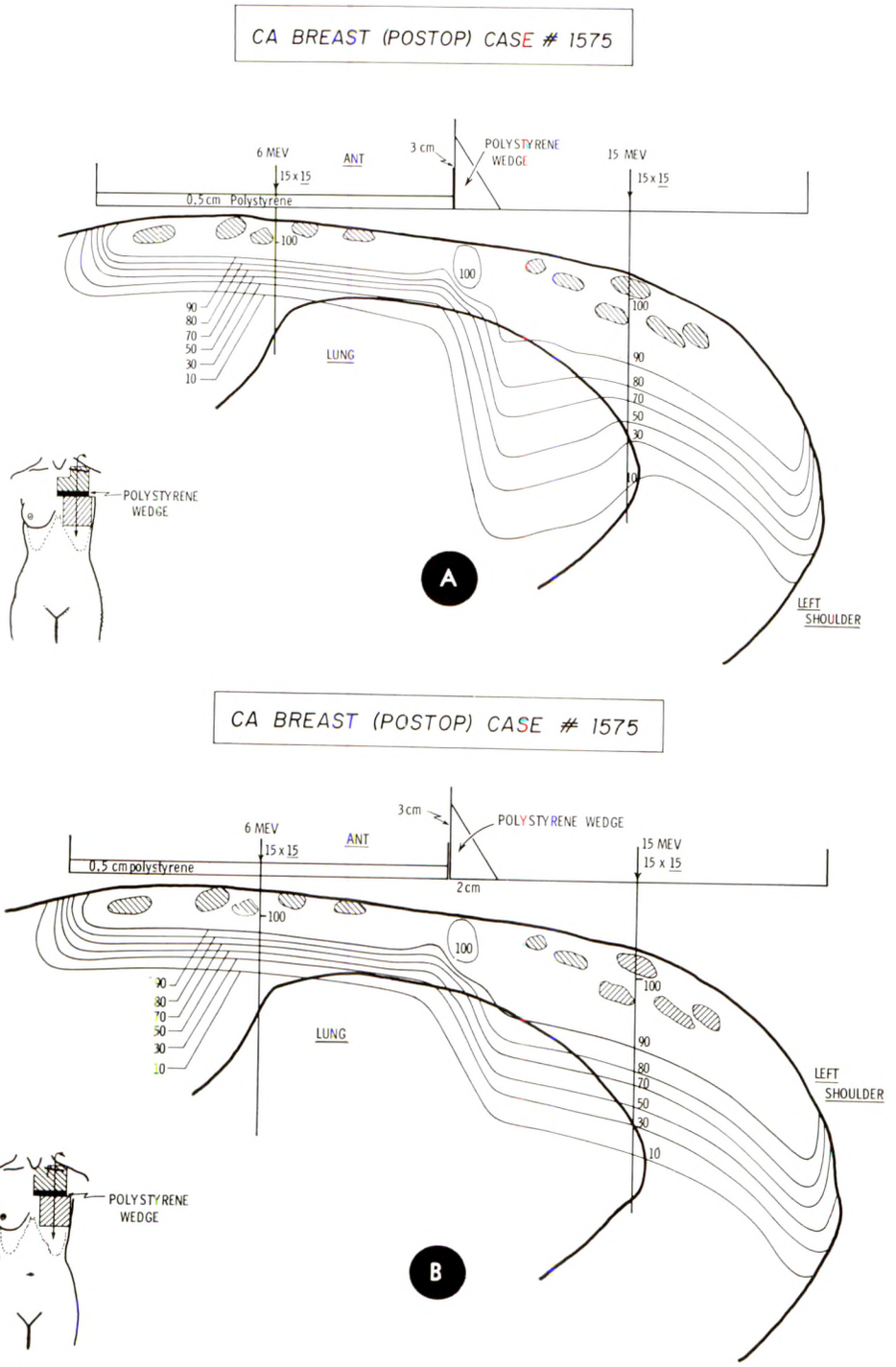


FIG. 9. (*A*) The plan illustrates some of the flexibility possible with control of energy and the use of plastic absorbers. (*B*) This plan indicates an apparently lower dose of the lung which would have been mistakenly assumed if the inhomogeneity correction system had not been applied.

lung dose due to its lower density is shown.

Figure 9*A* is the treatment plan for metastases following a left radical mastectomy. It should be noted that treatment with the electrons of different energies has made it possible to obtain a controlled dose distribution covering all of the known lesion and with limited exposure of the lung. The exposure of the lung here fully takes into consideration the lower density of the lung. If that had not been done we would have had a distribution as shown in Figure 9*B* which greatly underestimates the radiation exposure of the lung.

SUMMARY

High energy electrons have been used for cancer therapy since 1950, and clinical reports appear to confirm the utility of their advantageous physical features. A brief historic review of the treatment of electron dosimetry problems has included the development of methods of absorbed dose measurement. Intercomparison between centers have maintained dosage uniformity, and these procedures are now formalized in a published protocol. A major objective has been the achievement of realism on treatment planning. This necessitated phantom development so that measurement could be made of the influence on dose distributions by the inhomogeneous structure of the irradiated region. A system of treatment planning was developed which incorporated a procedure for correction of inhomogeneous absorption. The application of this system over the past decade has increased with greater availability of anatomic detail on individual cases. The physical bases of electron beam therapy, including dosimetry and physical aspects of treatment planning, are well established.

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PATTERNS OF USE OF 6-18 MEV. ELECTRON BEAM RADIATION THERAPY*

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RADIATION therapy deals with a variety of clinical situations, from control of primary lesions to relief of symptoms due to advanced disease. The degree of success achieved in providing local control of primary or metastatic disease is, in practice, related to the ability to deliver a localized dose of ionizing radiation. Low rates of local control, clumsy techniques, and excessive radiation reactions or complications with existing radiation modalities emphasize the need for a new therapeutic tool and stimulate its gradual integration into the practice of radiation therapy.

The working concept has not been to replace, for radiobiologic reasons, photons by electrons in the treatment of a particular category of disease or all tumors in certain anatomic areas. The aim has been to evolve a pattern of use of the 6 to 18 mev. electron beam consisting of treatment techniques of finesse and subtle fitting to clinical situations where satisfactory management had not been achieved.

The single characteristic of the electron beam which has provided the basis for its use is the rapid and sharp fall-off in depth dose (Fig. 1*A*). With 6 to 18 mev. electrons, the high dose level is reached within a millimeter of tissue; at 6 mev. the 80 per cent dose level decreases abruptly beyond 1.9 cm.; at 18 mev. an 80 per cent dose level is maintained to 4.7 cm. and drops to 20 per cent at 8 cm. This characteristic is of distinctive advantage in the treatment of malignant lesions of suitable anatomic location. A sterilizing dose of radiation can be delivered to the tumor while the total volume of tissue included in the high dose range is sharply limited. It is of interest to note that of 842 areas treated in 668 patients only slightly less than half were treated with energies above 12 mev. (Table 1).

Since the patterns of use have evolved from the strictly physical characteristics of the beam, there has been no hesitation to use electrons combined with photons (Fig. 1*B*) when this combination provides the proper volume distribution for particular anatomic distribution of disease. The selection of treatment technique and ratio of electrons to photons depends upon the maximum depth of the lesion to be treated. A variation of combination treatment is that of additional or "boost" therapy using reduced portals, in order to raise to a high level the total tumor dose to the initial gross disease. This practice is predicted on the hypothesis that microscopic disease can be permanently controlled with doses of the order of 5,000 rads in 5 weeks.

Table II shows the relative percentage of areas treated by the 3 modalities of electron beam technique.

CLINICAL APPLICATIONS

Table III shows the distribution by anatomic sites of 668 patients treated with the 6 to 18 mev. Siemens Betatrons at M. D. Anderson Hospital during 32 months from May 1, 1963 to December 31, 1965. More than half of the patients had lesions involving the upper respiratory and digestive tract. The majority of the remaining patients had carcinoma of the breast. Skin cancers and miscellaneous tumors of the trunk and the extremities make up the remainder of the cases.

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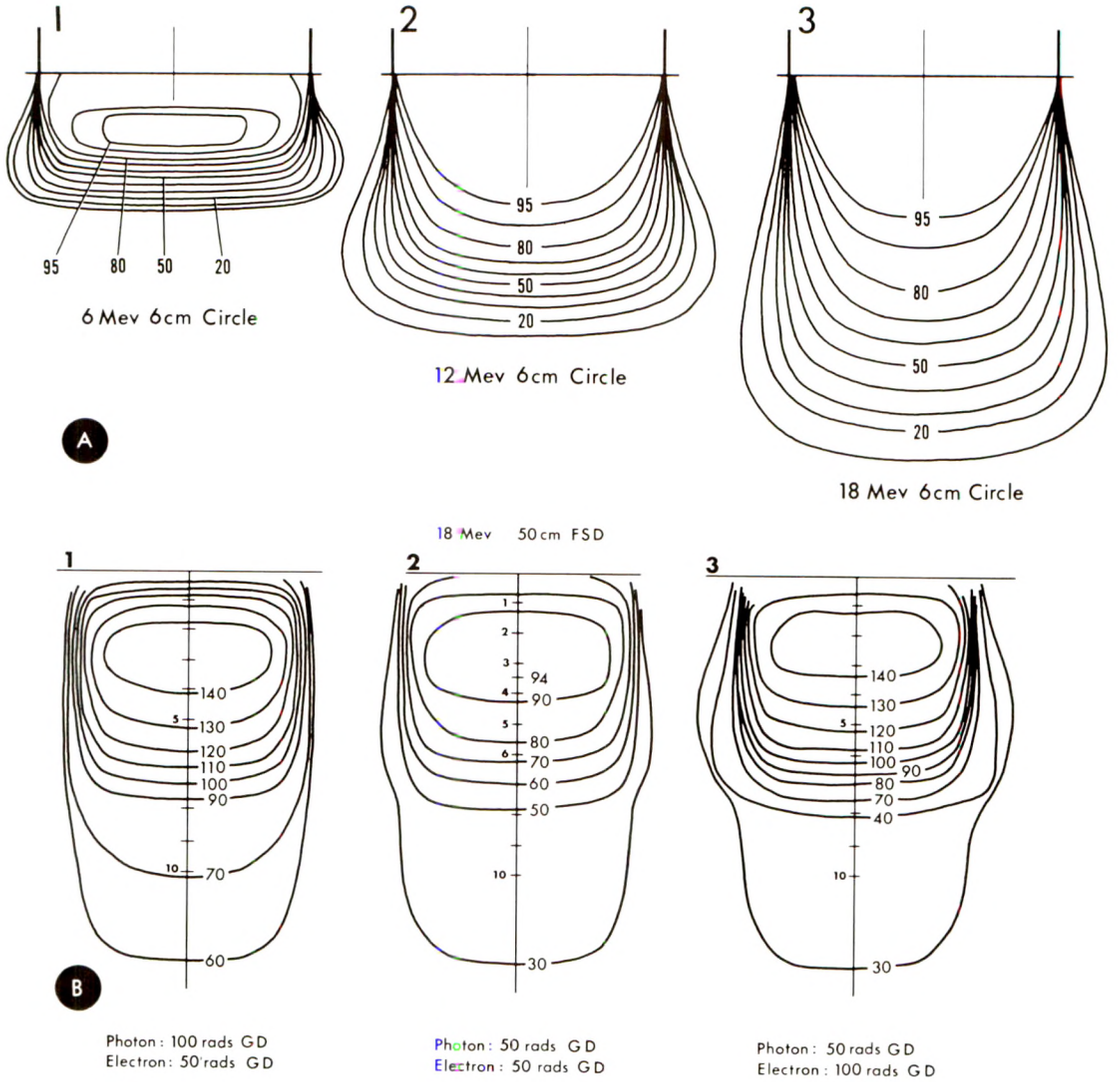


FIG. 1. (*A*) Electron beam isodose curves measured in a water phantom. Field size—6 cm. circle. (1) 6 mev. The 80 per cent curve is at 1.9 cm. There is little radiation beyond 2 cm. (2) 12 mev. The 80 per cent curve is at 3.6 cm. (3) 18 mev. The 80 per cent curve is at 4.7 cm. The decrease in percentage depth dose is less rapid than at 6 mev., but little radiation extends beyond 8 cm. Note that the 80 per cent isodose line is not flat at the geometric edge of the field. A generous field must be used. (*B*) Isodose curves for various combinations of photon and electron beam given doses (GD).

UPPER RESPIRATORY AND DIGESTIVE TRACT

Table IV gives the location of the primary lesions, in 286 patients, treated with the 6 to 18 mev. electron beam.

ORAL CAVITY

Lesions of the buccal mucosa, the gingivobuccal sulci, and the gingiva are satisfactorily treated to the desired tumor dose through a single homolateral portal. The

TABLE I

ENERGY RANGE IN 842 AREAS TREATED WITH 6–18 MEV. ELECTRON BEAM

(174 patients had more than one field treated)

6–12 mev.		15–18 mev.	
6 mev.	95 Areas	15 mev.	119 Areas
9 mev.	150 Areas	18 mev.	315 Areas
12 mev.	163 Areas		

Table II

TREATMENT TECHNIQUE WITH 6–18 MEV. ELECTRON BEAM

842 AREAS IN 668 PATIENTS

Technique	Areas
Electron Beam Alone	376
Electron Beam Combined with Other Radiation	156
Electron Beam Boost	310

Table III

DISTRIBUTION OF ANATOMIC SITES IN 668 PATIENTS TREATED WITH 6–18 MEV. ELECTRON BEAM

Oral Cavity	96	Cervical Lymph Nodes	
Oropharynx	106	Whole Neck	23
Hypopharynx	16	Small Neck Fields	29
Supraglottic Larynx	17	Boost to Lymph Nodes	72
Breast		Skin Cancer	72
Chest Wall	74	Miscellaneous	72
Peripheral Lymphatics	21		
Boost to Breast and Lymph Nodes	70		

skin reaction is not prohibitive because of the limited skin sparing of the electron beam. The acute mucous membrane reactions are brisk but are sharply localized to the area immediately adjacent to the tumor. No reaction is seen on the contralateral buccal mucosa, and the tongue is easily protected by an intraoral stent containing lead.

R.P., a 70 year old male, presented with a T_2 carcinoma of the posterior buccal mucosa, 2 cm. thick and 3 cm. in diameter. Treatment was given through an 8×8 cm. appositional field at 18 mev. with the final one-third of the dose given at 15 mev. In 6 weeks a tumor dose of 6,800–7,300 rads was delivered. The patient developed a heavy dry desquamation and a confluent exudate which was limited to the homolateral mucous membrane.

S.P., a 79 year old female, presented with a T_1N_0 exophytic lesion of the left upper posterior gingiva and hard palate. Treatment was given through a homolateral 6 cm. field with the 18 and 15 mev. electron beam. In $4\frac{1}{2}$ weeks the calculated dose at 4 cm. depth was 5,600 rads. The patient developed a moist desquamation and a confluent exudate limited to the posterior alveolar ridge and adjacent structures. A small, self-healing ulcer developed in the buccal

Table IV

LOCATION OF PRIMARY LESIONS OF THE UPPER RESPIRATORY AND DIGESTIVE TRACT

Treated with 6–18 mev. Electron Beam Alone or in Combination with Photon Beam

Oral Cavity	Primary Treatment	Boost Only	Oropharynx	Primary Treatment	Boost Only
Anterior 2/3 Tongue	17	4	Tonsillar Area	37	33
Floor of Mouth	40	1	Soft Palate and Uvula	2	1
Lower Gingiva	11		Base of Tongue + Valleculae	4	26
Buccal Mucosa	18	1	Glossopalatine Sulcus	2	1
Hard Palate and Upper Gingiva	4				
Hypopharynx	**Primary Treatment**	**Boost Only**	**Supraglottic Larynx**	**Primary Treatment**	**Boost Only**
Pyriform Sinus	4	3	Laryngeal and Lingual Epiglottis	3	5
Lateral Pharyngeal Wall	5	4	Pharyngo-epiglottic Fold	3	
			Aryepiglottic Fold	2	
			False Cord	4	
Glottic Larynx	1		Miscellaneous Head and Neck	40	10

mucosa at 4 months. At 30 months the oral mucous membrane was moist and there was no evidence of disease.

Lesions of the undersurface of the tongue and floor of the mouth are treated with the electron beam if they are not considered suitable for interstitial gamma-ray therapy alone. The electron beam may provide the entire treatment or may be combined with the photon beam through parallel opposing portals or with interstitial radium. Small lesions of the anterior floor of the mouth, including those with periosteal fixation or mandibular involvement, may be satisfactorily treated with the electron beam alone, either through a submental portal (Fig. 2) or an intraoral cone maintained in position by an intraoral stent, or with a combination of both.

P.H., a 46 year old female, presented with a T_3N_1 lesion of the anterior floor of the mouth fixed to the mandible. Treatment was given through a 7×4.5 cm. submental field at 18 mev. In $5\frac{1}{2}$ weeks the tumor dose was calculated to be 6,000 rads. The palpable neck lymph node received a given dose of 4,000 rads in 10 days. At the conclusion of treatment, the lesion in the floor of the mouth had disappeared. A right radical neck dissection was accomplished with no difficulty 3 weeks after treatment. At 28 months the patient was doing well with no evidence of disease.

TONSILLAR AREA

With high energy photon beam treatment, the control rate of T_1 and T_2 lesions of the retromolar trigone, anterior tonsillar pillar, and tonsillar fossa is approximately 90 per cent. This high control rate is achieved at the cost of complications in a significant number of patients. Common sequelae are exposed bone and some mandibular necrosis when either single homolateral portals or wedge paired filters are used and pronounced dryness of the mouth and throat with persistent impairment in the sense of taste when parallel opposing portals are used.

In an attempt to diminish the radiation dose to the oropharynx and the parotid on the opposite side, the electron beam has been used with varying ratios in the treatment plan. If the lesion is small and well lateralized, the electron beam is used alone, occasionally via an intraoral cone or through a single lateral portal. A 2:1 or 1:1 ratio of photon beam to electron beam through a homolateral portal is utilized in most lesions. By providing one-half of the tumor dose with the electron beam, the reaction is largely limited to the homolateral side and acute radiation morbidity and symptoms are decreased. In more deeply located lesions, following a basic 5,000 or 6,000 rads tumor dose with the high energy photon beam or Co^{60}, the electron beam may be used for additional irradiation ("boost") to reach a high tumor dose to a limited volume at the central primary site. The following cases illustrate each of the modalities:



Fig. 2. Patient with a floor of mouth lesion in treatment position for a submental field.

E.S., a 50 year old female, presented with a T_1 superficial lesion of the anterior tonsillar pillar extending onto the soft palate. Treatment consisted of 4,800 rads given dose with the 18 mev. electron beam via a 7×4.5 cm. homolateral field, 1,000 rads in 2 treatments via an intraoral cone at 6 mev., and 1,500 rads with the photon beam via a lateral field. The combined calculated tumor dose was 6,100 rads in

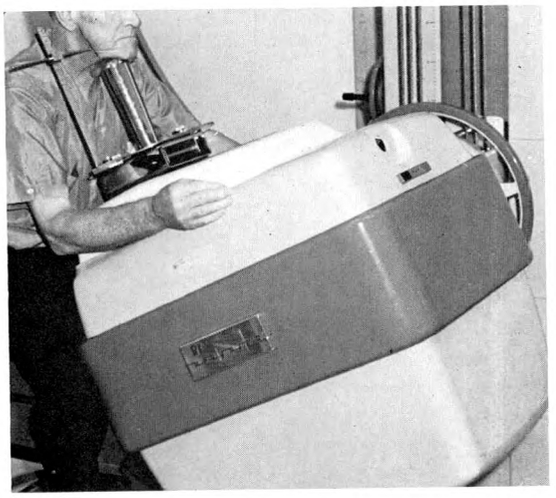


Fig. 3. G.S., a 56 year old patient with an extensive T_3N_0 lesion of the base of the tongue extending into the right glossopalatine sulcus and glossopharyngeal fold, received 6,000 rads tumor dose in 6 weeks through opposed, lateral Co^{60} fields. An additional 2,000 rads tumor dose was given with the 18 mev. electron beam through a submental field. The total dose was 8,000 rads in $7\frac{1}{2}$ weeks. At 27 months after treatment, the patient showed no evidence of disease. The soft tissues and mucous membrane are in good condition.

$4\frac{1}{2}$ weeks. At the conclusion of treatment there was a brisk mucosal reaction on the homolateral side with little reaction in the opposite oropharynx. At 24 months there was no evidence of disease and the skin and mucous membranes were in excellent condition.

A.D., a 47 year old female, presented with a T_2 lesion of the anterior tonsillar pillar with extension into the tonsillar fossa. At 4 cm. depth a tumor dose of 6,000 rads in $5\frac{1}{2}$ weeks was given with the 18 mev. electron and photon beams with a 1:1 tumor dose ratio. The 8×6 cm. field was decreased to a 6 cm. circle for the last week of treatment. In the fourth week of treatment, a confluent mucositis was confined to the right half of the oropharynx. At 23 months after treatment, the patient was free of disease and had normal taste and salivation. The mucous membrane was relatively normal in appearance and the treated skin was in good condition with no evidence of subcutaneous fibrosis.

R.V., a 51 year old female, presented with a T_1N_1 squamous carcinoma in the right tonsillar fossa with an enlarged lymph node at the angle of the mandible. A midline tumor dose of 5,000 rads was given with the Co^{60} unit through opposing lateral fields using a 2:1 loading in favor of the side of the lesion. Concurrently, the lower neck and supraclavicular areas were treated with Co^{60} through an anterior split field to a given dose of 5,000 rads. The patient was then transferred to the electron beam and received an additional 1,500 rads tumor dose at 4 cm. depth (1,875 rads exposure dose) given in 9 days through a 5 cm. circle at 18 mev. This brought the total tumor dose to 6,500 rads in $6\frac{1}{2}$ weeks. A radical neck dissection was performed 6 weeks after conclusion of treatment. At 10 months the patient was free of disease without dryness of the mucous membranes.

BASE OF TONGUE

The local control rate of T_3 and T_4 base of tongue lesions is approximately 60 per cent. The tumor doses which can be given through lateral portals, even though the fields are reduced towards the end of treatment, cannot exceed without prohibitive morbidity 6,500 to 7,000 rads in $6\frac{1}{2}$ to 7 weeks. The submental approach (Fig. 3) with the electron beam avoids the already heavily irradiated mandible. By this technique, tumor doses of 7,500 to 8,500 rads in 7 to $7\frac{1}{2}$ weeks may be achieved with the possibility of improved local control without increase in complications.

PHARYNX AND LARYNX

Selected lesions of limited extent of the lateral pharyngeal walls, false cords, pharyngo-epiglottic folds, and occasionally of the pyriform sinus and lingual surface of the epiglottis may be satisfactorily treated with a single appositional electron beam field. With this technique the rapid drop-off in depth dose of the electron beam diminishes the dose to the total laryngeal structures and should yield a decrease in the incidence and severity of laryngeal edema.

S.H., a 52 year old male, presented with a squamous cell carcinoma of the right false cord with extension to the base of the epiglottis. A calculated minimum tumor dose of 6,600 rads in $5\frac{1}{2}$ weeks was given through a 6×5 cm. electron beam appositional portal reduced to 4×4 cm.

for the last week of treatment. At the completion of treatment, there was minimal edema of the arytenoids with moderate mucositis. At 26 months there was no evidence of disease and the patient had an excellent voice. There was some fibrosis of the subcutaneous tissues.

NECK LYMPH NODES

The management of cervical lymph node metastases continues to be a challenging problem to the radiation therapist. When the lymph nodes are small and single, excellent results are achieved with radical neck dissection. When a radical neck dissection is performed for multiple or large lymph nodes, the risk of carcinomatosis in the neck is high. If there is recurrence following radical neck dissection, only rarely is the recurrence evidenced by a single nodule and, therefore, the entire neck must be treated. This very large area is difficult to treat satisfactorily with any technique other than a single large appositional field. The electron beam at 9 mev. or occasionally 12 mev. will efficiently treat the whole neck (Fig. 4). The area to be included extends from the clavicle to the mastoid tip and incorporates the submental tissues as well as the posterior cervical chain. The enhanced skin sparing effect at the lower energies permits the delivery of 6,000 rads in 5 weeks with a skin reaction which rarely exceeds dry peeling. With this technique, laryngeal edema, even following radical neck dissection, is usually minimal and temporary.



Fig. 4. This 60 year old patient with a history of multiple carcinomas of the skin of the head and neck, had a radical neck dissection for enlarged left neck lymph nodes. Tumor was found infiltrating the connective tissues of the neck. The whole neck was treated with the electron beam at 12 mev. and 9 mev. to an exposure dose of 6,000 rads in $4\frac{1}{2}$ weeks. At the conclusion of treatment, there was moderate erythema of the treated skin with dry desquamation and moderate edema of the left arytenoid and aryepiglottic fold. At 18 months, the skin of the left neck was in excellent condition and there was essentially no edema of the left hemilarynx. At 24 months the patient was found to have metastatic squamous carcinoma presenting in the suboccipital portion of the neck, adjacent to a grafted area, well outside the original field. This area was treated with the electron beam at 9 mev. to a given dose of 6,500 rads in 6 weeks. The skin showed dry desquamation at the conclusion of treatment.

When the metastatic lymph nodes are inoperable and are to be treated by irradiation alone, additional "boost" therapy following treatment of the primary lesion in conjunction with the lymph nodes is necessary if permanent control of these lymph nodes is sought. In the process of treating the primary lesion, a tumor dose of 5,000 to 6,000 rads to the whole neck has usually been given. In the past, radioactive gold grain or interstitial radium implants have been utilized but frequently were found to be unsatisfactory because of the nonhomogeneous distribution of the radioactive material. The incidence of complications, such as infection, was high when interstitial therapy was applied after extensive irradiation of the neck. With the electron beam, residual palpable disease is treated through small portals at 9 to 12 mev., or occasionally 15 mev. initially, to achieve a total tumor dose of 8,000 to 10,000 rads. Metastatic disease in lymph nodes rarely will fail to respond to such high dosage.

H.G., a 68 year old male with a history of carcinoma of the lip excised one year previously, presented with a large submandibular lymph node fixed to the mandible. Because of severe emphysema, a radical neck dissection was not possible. The entire neck was treated

TABLE V

TREATMENT OF CERVICAL LYMPH NODES WITH 6–18 MEV. ELECTRON BEAM

120 Patients

Technique	Patients
Whole Neck Fields	18
Small Neck Fields	23
Boost Fields	69
Miscellaneous Neck Fields	10

with a large electron beam field, the lower neck at 9 mev. and the upper neck with the enlarged lymph node at 15 mev. The lower neck received an exposure dose of 5,700 rads in 4 weeks. The submandibular lymph node received, through gradually reduced fields, a total exposure dose of 9,200 rads in 6½ weeks. A heavy dry desquamation developed which was healed at 6 weeks.

The patient then developed a metastatic submandibular lymph node on the opposite side. The electron beam at 12 mev. was used to treat the upper half of the neck and through gradually reduced fields the submandibular area received a total exposure dose of 8,100 rads in 6 weeks. An area of moist desquamation was well healed at 6 weeks. The patient was free of disease at 6 months and the neck tissues have remained in good condition without fibrosis.

Table v shows the distribution by treatment situations of patients with metastatic neck disease.

BREAST

The electron beam has extensive use in the treatment of carcinoma of the breast. Table vi shows the distribution of patients by treatment situations. The supraclavicular and internal mammary chain areas are treated, after radical mastectomy, with the electron beam at 12 and 15 mev. respectively. If the axillary lymph node involvement is more than minimal or if there is skin disturbance associated with the primary lesion, the entire chest wall is treated with the electron beam at 6 mev., occasionally at 9 mev., concurrently with the peripheral lymphatics (Fig. 5). For chest wall recurrences, the entire chest wall is included in the field; 6 or 9 mev. is used depending on the thickness of the disease.

The total skin area is large but skin reactions have not been severe in the majority of cases. The moist reactions seen with large chest wall fields treated at the lower mev.s are usually limited in extent and heal rapidly. At 12, 15, and 18 mev. the skin sparing is less. With the present techniques employed, the incidence of pulmonary symptoms and radiation pneumonitis has been low. High energy electrons penetrate deeply in aerated tissue, but at 6 mev. most of the radiation is absorbed in the chest wall.

The electron beam has been used for the administration of "boost" doses to residual masses in the breast and axilla after protracted radical irradiation has delivered a basic tumor dose of 5,000 to 6,000 rads. These additional doses have ranged from 2,400 to 4,000 rads (Fig. 6). The energy level used depends upon the depth dose de-

TABLE VI

CARCINOMA OF BREAST TREATED WITH 6–18 MEV. ELECTRON BEAM

180 Patients

Electron Beam Alone or with Cs^{137} to Peripheral Lymphatics		Boost	
Chest Wall (large field)	65	Boost to Breast Primary	27
Immediate Post Radical	42	Boost to Axillary Lymph Nodes	10
Chest Wall Recurrence	23	Boost to Primary and Axilla	30
Chest Wall (small field)	9	Miscellaneous	3
Peripheral Lymphatics	21		
Miscellaneous	15		

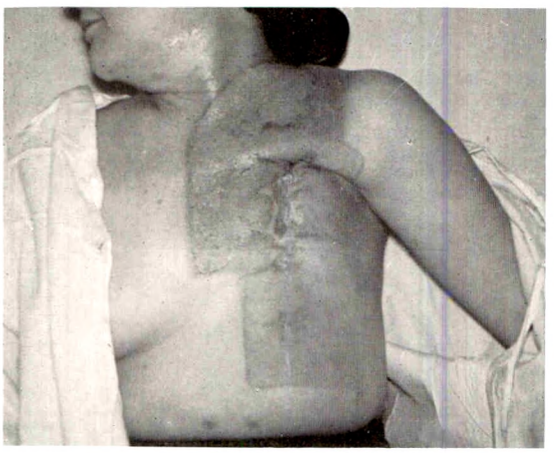


Fig. 5. This 41 year old female had a left radical mastectomy for a mass located in the subareolar area. In the operative specimen, 14 of 31 axillary lymph nodes were positive. The patient had poor healing of the mastectomy wound, particularly in the infraclavicular fold, and irradiation was delayed for 2 months to permit 2 grafting procedures. The supraclavicular area was treated at 12 mev. with an exposure dose of 5,400 rads in $3\frac{1}{2}$ weeks. The internal mammary chain was treated at 15 mev. to an exposure dose of 5,650 rads in $3\frac{1}{2}$ weeks. The entire chest wall, using contiguous 12×10 cm. fields, was treated at 6 mev. to an exposure dose of 6,000 rads in 4 weeks.

The patient had patchy moist desquamation of the supraclavicular and internal mammary fields which healed in 7 to 9 days. The chest wall reaction was less pronounced, as expected, since the surface dose was less at 6 and 9 mev. At 4 months all areas were well healed and the skin tanning was decreasing.

sired. The incidence of severe acute skin reactions and late necrosis has been low even with these high tumor doses.

CONCLUSION

The 6 to 18 mev. electron beam has been shown to have unique value in a Radiation Therapy Department with a large patient population presenting with a variety of lesions. The rapid build-up and sharp drop-off in tissue dose permit a precision and nicety of dosage not easily reproducible with other approaches. The electron beam has proven to be an ideal irradiation modality in the carefully selected situations.

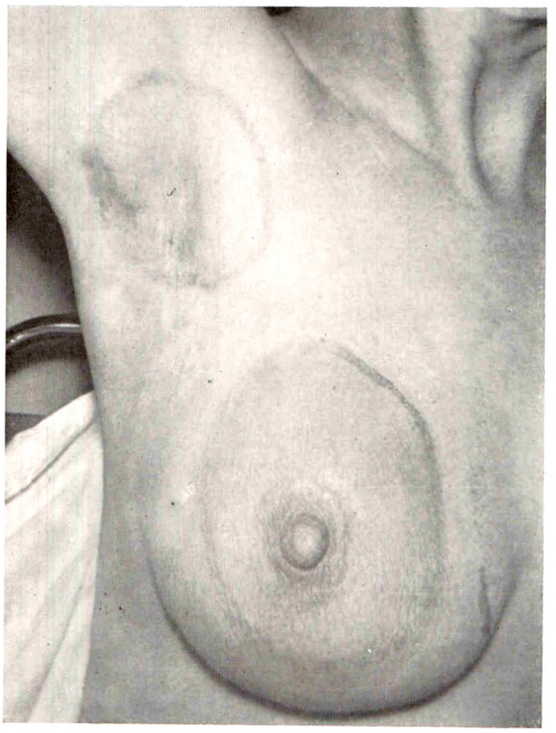


Fig. 6. This 55 year old female received Co^{60} treatment through comprehensive fields for inoperable carcinoma of the breast with axillary lymph node metastases. At the end of 8 weeks, the primary breast mass had received 6,000 rads tumor dose. The midpoint of the axilla had received 5,000 rads tumor dose in 5 weeks. Boost treatment was then given with the electron beam to the residual masses in the breast and axilla. Because of the thickness of the lesions, the 18 mev. beam was used to deliver 3,850 rads to the breast and 3,300 rads to the axilla. The patient developed moist desquamation of both areas but healing occurred within 3 weeks.

The fundamental characteristic of rapid attenuation of depth dose is less with higher energies and a significant tissue dose is delivered to the deeper structures. With parallel opposing portals at 25 mev. or more, the volume distribution offers no physical advantage over the photon beam.

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HIGH SPEED ELECTRON BEAM THERAPY*

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THE use of direct electron therapy instead of the indirect way by means of electromagnetic rays was already tried some 40 years ago. The radiotherapists at that time most probably knew that the biological effect was produced by the electrons, as Glocker[4] so strongly emphasized in 1935. The first physical experiments took place in the south of Switzerland, at Monte Ceneri, noted for numerous lightning storms, because the high energies needed were not yet available. The basic experiments in the development of the Röntgen machine in the million volt range were also performed there. Two of the engineers, Brasch and Lange,[2] wrote at that time about the favorable conditions of absorption using high volt electrons (HVE). They discussed the great advantages of irradiation with HVE in comparison to photon therapy, recommended the grid technique to protect the superficial layers, and described the increased dose beneath the skin—all facts, which were realized some decades later again.

Due to technical developments, today it is possible to reach any necessary depth by using HVE. We are all aware of the rapid fall-off which can be chosen arbitrarily by changing the voltage. Its beneficial effect on sensitive tissues, such as the spinal cord (which must be kept from an overdose of radiation) is well known. This area can only be protected by the use of complicated methods when employing conventional rays. The smaller integral dose is important because of the reduced general reaction.

High speed electrons are especially valuable when the tumor extends from the surface to a certain depth and a one field technique is desirable. Unfortunately, this rapid fall-off flattens out at increasingly higher energies so that the conclusion might be drawn that electron beam irradiation is indicated only in superficial and medium deep therapy.

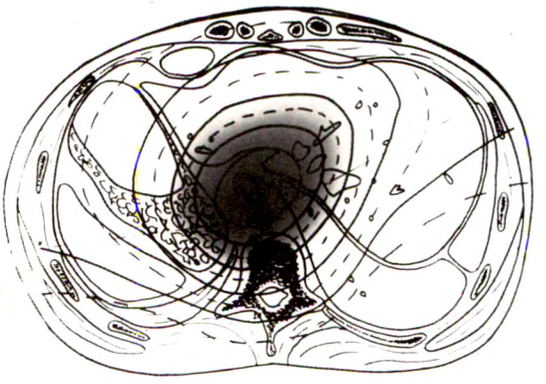


FIG. 1. Arc therapy in postoperative irradiation of stomach cancer. Energy, 35 mev. betatron; field, 6×10 cm.; rotation angle 170°; depth of rotation center 15 cm. Irradiation with 6,630 r in the 80 per cent isodose in 62 days was given and well tolerated.

USE OF ARC AND ROTATIONAL THERAPY OR OF AN ELECTRONIC LENS

Newer techniques, consisting of the use of arc and rotational therapy or of an electronic lens help overcome this disadvantage. They enable administration of a suitable depth dose with adequate protection of the superficial normal structures and the deeper radiosensitive tissues at higher energies, even surpassing the good effect of photon therapy.

Figure 1 shows the isodose curve and distribution of arc therapy in a case of postoperative carcinoma of the stomach where the dose is concentrated in the prevertebral lymph node area. Although our experience with rotational therapy is limited, we feel that it is possible to treat a postoperative stomach carcinoma prophylactically with little or no effect on the

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general condition or the gastrointestinal tract of the patient.

In cases which are anatomically unfavorable for rotational therapy, such as in bladder carcinomas, we use the electronic lenses because of the better concentration of the dose than achieved with rotational therapy (Fig. 2). The lens, of course, is not used throughout the entire therapy; only about one-half of the dose is given in this manner during the last half of irradiation. In this way, we have been able to reduce undesirable local and general reactions.

ADVANTAGES OF HIGH SPEED ELECTRON BEAM THERAPY

The advantages of high speed electron beam therapy have previously been published.[9–21]

There are also disadvantages which can be corrected, and situations in which electron beam therapy might be contraindicated. The reader is referred to the Montreux Symposium on high speed electrons which was held in 1964.[3,18,19,20]

The physical advantages alone would justify having a high speed electron unit in a large tumor center, but there are also some clinical observations, which prove that, at least in certain tumor situations, electrons are more advantageous than photons. Schubert,[6] for example, stated in 1950 that he was able to cure carcinoma of the vulva, indicating that electron therapy provided a new approach. With photons and the same physical conditions, treatment of this lesion was impractical because of the resultant severe local reaction.



Fig. 2. Isodose distribution in sagittal plane with electronic lens in a cancer of the bladder treated with 34 mev.

Since then, further experience has shown additional biologic advantages of high speed electron beam therapy. Some of these, from different points of view, are listed below.

1. It is easier to control tumors which are situated in a radiosensitive area. Oberheuser *et al.*[5] confirmed the observation of Schubert[6] concerning carcinomas of the vulva. Becker and Schubert[1] presented similar results, which were about equal to the best surgical results obtained in Sweden, using electrocoagulation followed by postoperative irradiation. These results are impressive inasmuch as Schubert[6] treated far advanced cases which had a poor prognosis when the older methods were employed.

In carcinomas of the penis, the results are even more impressive. Figure 3*A* shows a case of an 80 year old man who presented with bilateral inguinal metastases which were fixed and ulcerated on one side. He was treated with a dose of 8,400 r in 41 days (22 mev.) to the left inguinal region. The primary tumor was treated in 2 series and healed. Figure 3*B* shows the inguinal region $3\frac{1}{2}$ years later.

Inflammatory tissue is quite sensitive and must be carefully considered during radiation treatment. However, relatively good results were obtained in treating carcinoma of the ear associated with perichondritis. Another case, one of squamous cell carcinoma of the larynx, with an incised abscess and a tracheotomy was referred for treatment to us. A dose of 8,400 r in 41 days was delivered, using 22 and 30 mev. Later, it was possible to remove the



Fig. 3. Fixed ulcerated metastases in cancer of the penis. Irradiation with 8,400 r, 22 mev. electrons in 41 days. (*A*) Before treatment. (*B*) Three and one-half years later. Slight induration. (Reproduced with permission of Butterworths, Publishers, London, England, from Modern Trends in Radiotherapy.)

tracheotomy tube. Figure 4 shows the patient 6 years following treatment with only a small amount of telangiectasis and induration. He is well and working, 7 years after treatment. Thus it appears that some cases of cancer of the ear and intrinsic larynx with inflammatory perichondritis can be cured without producing necrosis of the cartilage.

2. Attempt at curative treatment of a local recurrence after irradiation is associated with much risk even when using high speed electrons; however, good results have been obtained in skin and breast cancers and other superficially localized lesions. As an example, Figure 5*A* shows a 21 year old female who has been receiving radiation therapy for the past 5 years because of Hodgkin's disease. A large area of recurrence is seen in the irradiated skin with telangiectasis and pigmentation after an approximate dose of 4,500 r of conventional roentgen rays $4\frac{1}{2}$ years earlier. A dose of 6,000 r in 23 days with a 20 mev electron beam was delivered to the same area. Figure 5*B* shows the patient 3 years after treatment. No further skin changes appeared. As a rule, we recommend surgery for radiation recurrences. If the curative chances are nil or small, an attempt employing high speed electrons is indicated. It seems that the prognosis is better with electron than with photon therapy.

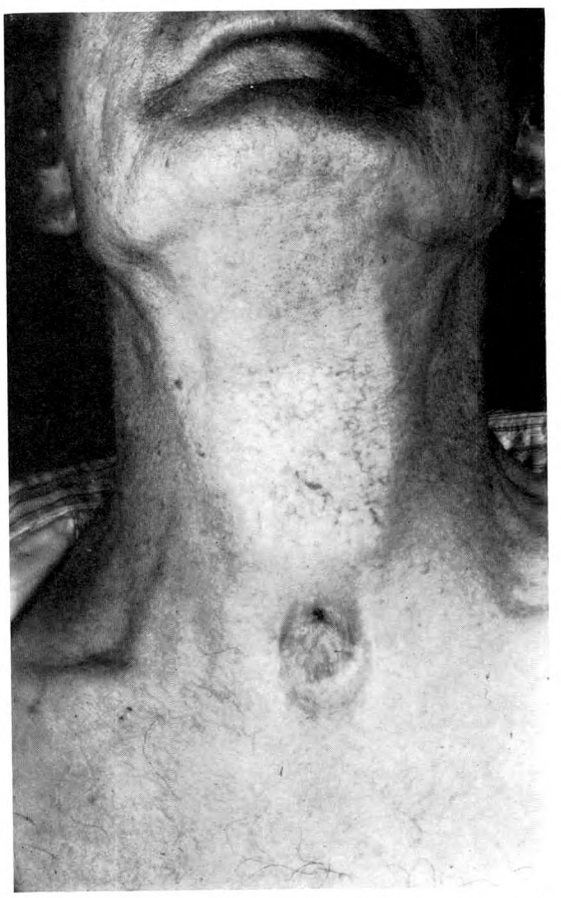


Fig. 4. Infiltrating laryngeal carcinoma with perichondritis and pus formation in a male, 66 years of age. Incision and tracheotomy. Irradiation with 22 and 30 mev. electrons to 8,400 r in 41 days resulted in disappearance of the carcinoma and closure of the tracheotomy. Patient is in good health 6 years later. (Reproduced with permission of Georg Thieme Verlag, Stuttgart, Germany, from Elektronentherapie.[17])



Fig. 5. (*A*) Hodgkin's disease in a 21 year old woman. Local recurrence after irradiation with 4,460 r using conventional roentgen rays $4\frac{1}{2}$ years earlier. (*B*) Three years after electron beam therapy, using 6,100 r in 23 days with 20 mev. (Reproduced with permission of Georg Thieme Verlag, Stuttgart, Germany, from Elektronentherapie.[17])

3. The reaction of irradiated tissue to additional trauma is a criterion for the evaluation of damage. We felt that we could answer the question whether tissue damage would be less severe using high speed electrons than conventional high voltage radiation, by systematic pre-irradiation of malignant tumors. For many years, we have been proponents of two methods of pre-irradiation.

(a) Operable tumors. A low dose of high speed electrons of 4,000 r in 10 days is delivered. This would represent a dose of 2,400–3,000 r of conventional roentgen rays using an RBE of 0.7. In children or in very sensitive tumors, we use a lower dose. Surgery follows after a few days to 2 weeks at the latest.

(b) Inoperable or borderline tumors. In these we give higher doses—if possible 6,000 r with an interval of 6 to 8 weeks until surgery. My co-worker Campana[3] reported about 157 cases which received radiation therapy previous to surgery since 1958, using high speed electrons. Surgery did not prove to be more difficult because of the pre-irradiation. The interval between radiation therapy and surgery, however, should not be extended any longer than 2 months, since after that fibrotic changes set in rendering operation more complicated. The postoperative course in these cases was comparable to that of the nonirradiated patients, except that it is advisable to leave the sutures in the skin longer. When doses above 6,000 r are delivered, rather marked complications may be noted. No comparison can be made with past results, since formerly only cases considered inoperable were given radiation therapy prior to surgery. This is no longer true and what is particularly impressing is to see that skin transplants are taking after doses of up to 6,000 r.

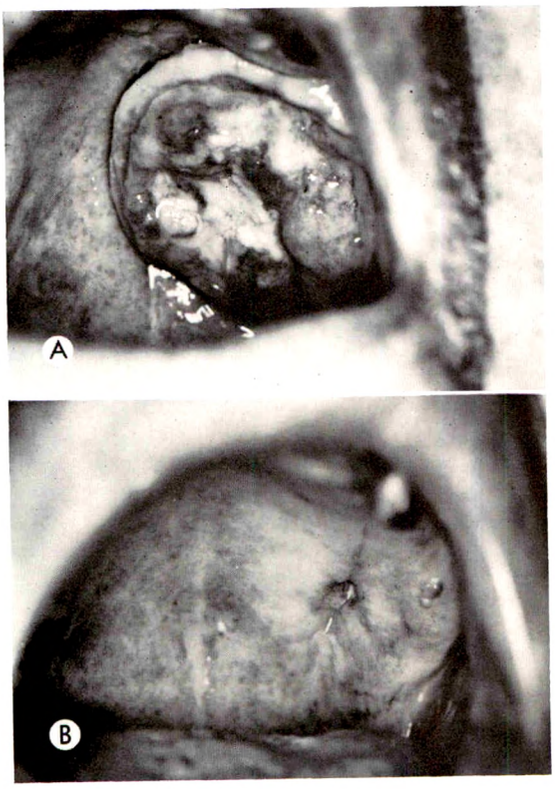


Fig. 6. Cylindroma of the hard palate in a 70 year old man. Irradiation with 20 mev. electron beam to 8,070 r in 35 days, and a supplementary dose of 2,100 r in 10 days, 1 month later. There was slow shrinkage of the tumor and the patient is free of disease $3\frac{1}{2}$ years later. (*A*) Before treatment. (*B*) Two years after treatment. No signs of disease. (Reproduced with permission of Georg Thieme Verlag, Stuttgart, Germany, from Elektronentherapie.[17])

4. Many observations show that tumors which were considered resistant to radiation could be treated more favorably with electrons. The mixed parotid tumors are an example. Becker was the first to note this and his results were confirmed by us. It appears now that postoperative recurrences, which are difficult to control in this lesion can probably be avoided.

Primary surgery with loss of the facial nerve in cases of parotid carcinoma is no longer acceptable. We apply 20 or 25 mev. electron beam therapy according to the extent of the tumor, otherwise a deep seated recurrence may develop. Closely related to the mixed tumor of the parotid is the cylindroma, an example of which is shown in Figure 6, *A* and *B*, before and after treatment, respectively. The papillary form of thyroid cancer is considered to be radioresistant, but this is not the case when

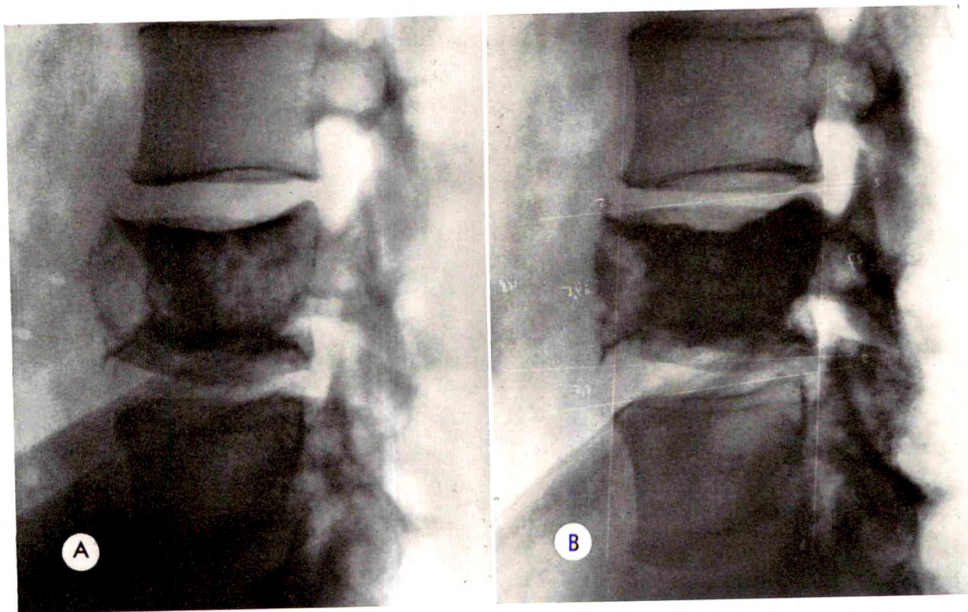
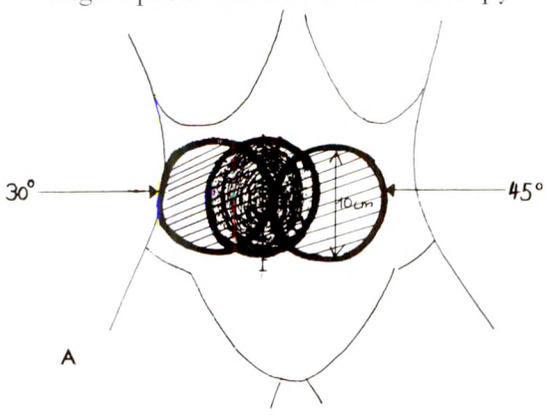


Fig. 7. Chordoma of the 4th lumbar vertebra in a 43 year old man, histologically verified by exploratory laparotomy. Irradiation with 7,800 r in 42 days with 30 mev. electron beam. The patient is free of disease 3 years later. (*A*) Lumbar spine at the beginning of treatment. (*B*) Two and three-quarters years later.



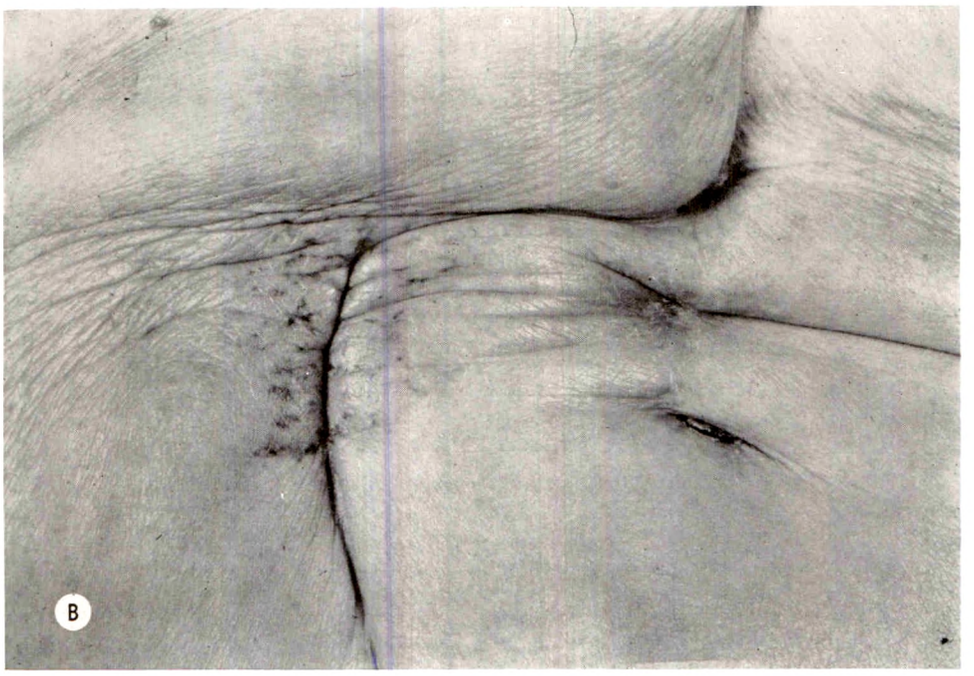


FIG. 8. Implant metastasis in abdominal scar in a case of adenocarcinoma of the colon, ½ year after radical operation. The mass was 8×10 cm. and 7 cm. deep. The irradiation was carried out in 2 series. (*A*) Schema of plan of treatment. *First series:* 30 mev.; right side (30° angle) 2,845 r; left side (45° angle) 2,845 r; or a total of 5,690 r. *Second series:* 22 mev. (direct); 2,790 r. The total dose was 8,480 r in 62 days. (*B*) No sign of disease 8 years later. Operation for duodenal ulcer 10 months after irradiation showed cure of the primary lesion.

electron beam therapy is used. Of course, operable cases should have surgery, but, in inoperable cases and in recurrences, electron beam therapy is the treatment of choice. Three cases of Hürthle cell carcinomas with incomplete surgery and recurrence were also treated and are free of disease from 2½ to 4 years.

The favorable results obtained in cases of fibrosarcoma and, above all, the surprising results achieved in synovioma are especially worthy of mention. Cases of resistant chordoma have also shown improvement. The patient in Figure 7, *A* and *B*, was treated only with electron beam irradiation, and was symptom free for a period of 3 years. Uhlmann and Ovadia[8] reported good results in bronchial carcinoma. They described 8 cases out of a total of 30 of inoperable tumors which were free of disease for over a 2 year period. Schumacher[7] of Berlin confirmed their results. He recommends a special technique of treatment, once or twice a week. His results with in-

operable cases equal those of surgeons who have operated in much earlier stages. Cases of tumors of the gastrointestinal tract which were considered to be radioresistant also have shown some good results. One such case is demonstrated in Figure 8, *A* and *B*. A large abdominal wall implant metastasis of an adenocarcinoma of the ascending colon ½ year following surgery was experimentally irradiated with electron beam. A total dose of 8,480 r in 82 days was delivered in 2 series, after which the tumor disappeared. Later, the patient was again operated on because of a duodenal ulcer, and no tumor was found at surgery. The patient is living and well almost 8 years following radiation treatment. In general, however, we recommend only preoperative irradiation because of the extreme sensitivity of the mucosa of the gastrointestinal tract.

CONCLUSION

We believe that high speed electron beam therapy is an advancement in the fight against cancer and should be included in the arsenal of weapons.

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TISSUE COMPENSATING FILTERS FOR COBALT 60 TELETHERAPY*

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SKIN sparing, an important advantage of radiotherapy with high energy radiation sources such as Co^{60}, will be lost if bolus is used. Since adequate treatment planning at times requires shaping the beam entrance surface, a substitute for bolus is needed. Ellis, Hall and Oliver[1] have described tissue compensating filters which may be used as bolus substitutes. These filters are positioned 15 cm. or more above the patient's skin to not disturb the dose buildup below the skin surface. The filters are constructed of small aluminum or brass blocks. The thickness of the blocks multiplied by their density originally equalled the thickness of tissue equivalent bolus required to convert an irregular patient contour into a surface perpendicular to the central axis of the incident radiation beam. Conversions between air distances and brass thicknesses were later modified by Hall and Oliver[2] to correct for loss of scattered radiation when compensators are used. The method of these investigators includes construction of a plaster cast of the patient. Air distances for which tissue compensation is desired are measured on this cast. The present report describes modifications of the original method which permit more convenient measurement of air distances and more rapid assembly of tissue compensating filters.

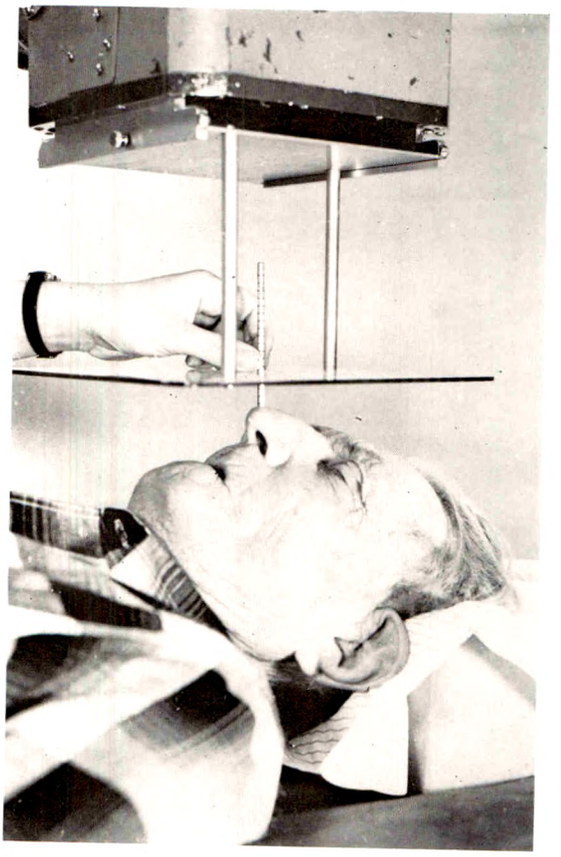


FIG. 1. Measurement to the nearest 0.1 cm. of air gaps beyond the 80 cm. source skin distance. This patient is to be treated for carcinoma of the maxillary antrum. Measuring rod includes correction for 2 cm. displacement of the lucite plate above the source skin distance. Holes are spaced at 2.0 cm. intervals in the plate used for the 80 cm. source skin distance. Holes in the lucite plate for the 95 cm. source skin distance are 2.4 cm. apart.

METHOD

Construction of plaster casts is time consuming and uncomfortable for the patient, and may be bypassed by measuring air distances for which compensation is desired directly on the patient. One of the collimator attachments with which these measurements are made is shown in Figure 1. The patient is positioned so that the highest point on the skin area to be irradiated is at the selected source skin distance. Two centimeters above this point a 1/8 inch thick lucite plate is held perpendicular to the beam central axis by rods extending

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TABLE I

CONVERSIONS BETWEEN AIR DISTANCES FOR WHICH COMPENSATION IS DESIRED AND THICKNESSES OF BRASS BLOCKS IN TISSUE COMPENSATING FILTERS

(Co^{60} teletherapy; SSD, 80 cm.; source compensating distance, 62 cm.)

Air Distance (cm.) (Corrected*)	Brass Thickness (mm.)	Air Distance (cm.) (uncorrected†)
0.0 0.3	0	0.0– 0.4
0.4– 1.1	1	0.5– 1.3
1.2– 1.7	2	1.4– 2.1
1.8– 2.3	3	2.2– 2.9
2.4– 3.0	4	3.0– 3.8
3.1– 3.8	5	3.9– 4.6
3.9– 4.3	6	4.7– 5.5
4.4– 4.9	7	5.6– 6.3
5.0– 5.5	8	6.4– 7.1
5.6– 6.2	9	7.2– 8.0
6.3– 6.8	10	8.1– 8.8
6.9– 7.5	11	8.9– 9.7
7.6– 8.0	12	9.8–10.5
8.1– 8.6	13	10.6–11.3
8.7– 9.3	14	11.4–12.2
9.4– 9.9	15	12.3–13.0
10.0–10.5	16	13.1–13.8
10.6–11.2	17	13.9–14.7
11.3–11.8	18	14.8–15.5
11.9–12.5	19	15.6–16.4
12.6–13.1	20	16.5–17.2

* Corrected air distances were obtained by adding small amounts of brass to compensating filters until resulting isodose curves were acceptable.

† Uncorrected air distances are the products of brass density and ±0.5 mm. of the corresponding brass thickness.

from an aluminum plate attached to the collimator. A pencil-like aluminum rod graduated in 0.5 cm. increments is extended through holes in the lucite plate until it touches the patient's skin. Air distances for which compensation is desired may be interpolated to the nearest 0.1 cm. The scale on the measuring rod includes correction for displacement of the lucite plate above the source skin distance. From these measurements a tissue compensating filter is constructed by attaching brass blocks to an aluminum plate with masking tape coated with adhesive on both sides. About 20 minutes is required for a technician to measure air distances on the patient and construct a compensating filter for one field.

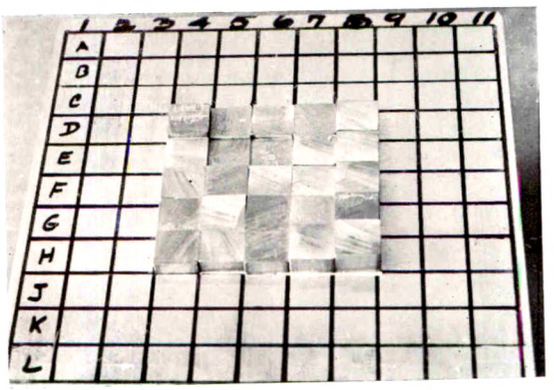


FIG. 2. Tissue compensating filter constructed for 1 (right anterior) of 2 fields used during radiotherapy of carcinoma of the maxillary antrum.

Using a tissue compensating filter results in a smaller contribution of scattered radiation to the total dose at any point within the patient than if bolus were used. Inadequate compensation is obtained if thicknesses of brass blocks are calculated by dividing air distances by the density of brass. Improved compensation can be achieved by first constructing a compensator for an irregular surface of a water phantom. The filter is made with brass blocks of thicknesses calculated by dividing air distances by the density of brass (8.4 gm./cm.^{3} for brass used here), then adding small thicknesses of brass to the com-

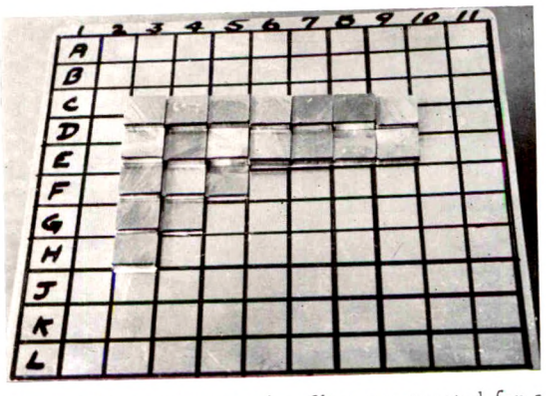


FIG. 3. Tissue compensating filter constructed for 1 (left posterior oblique) of 3 fields used during radiotherapy of carcinoma of the upper third of the esophagus.

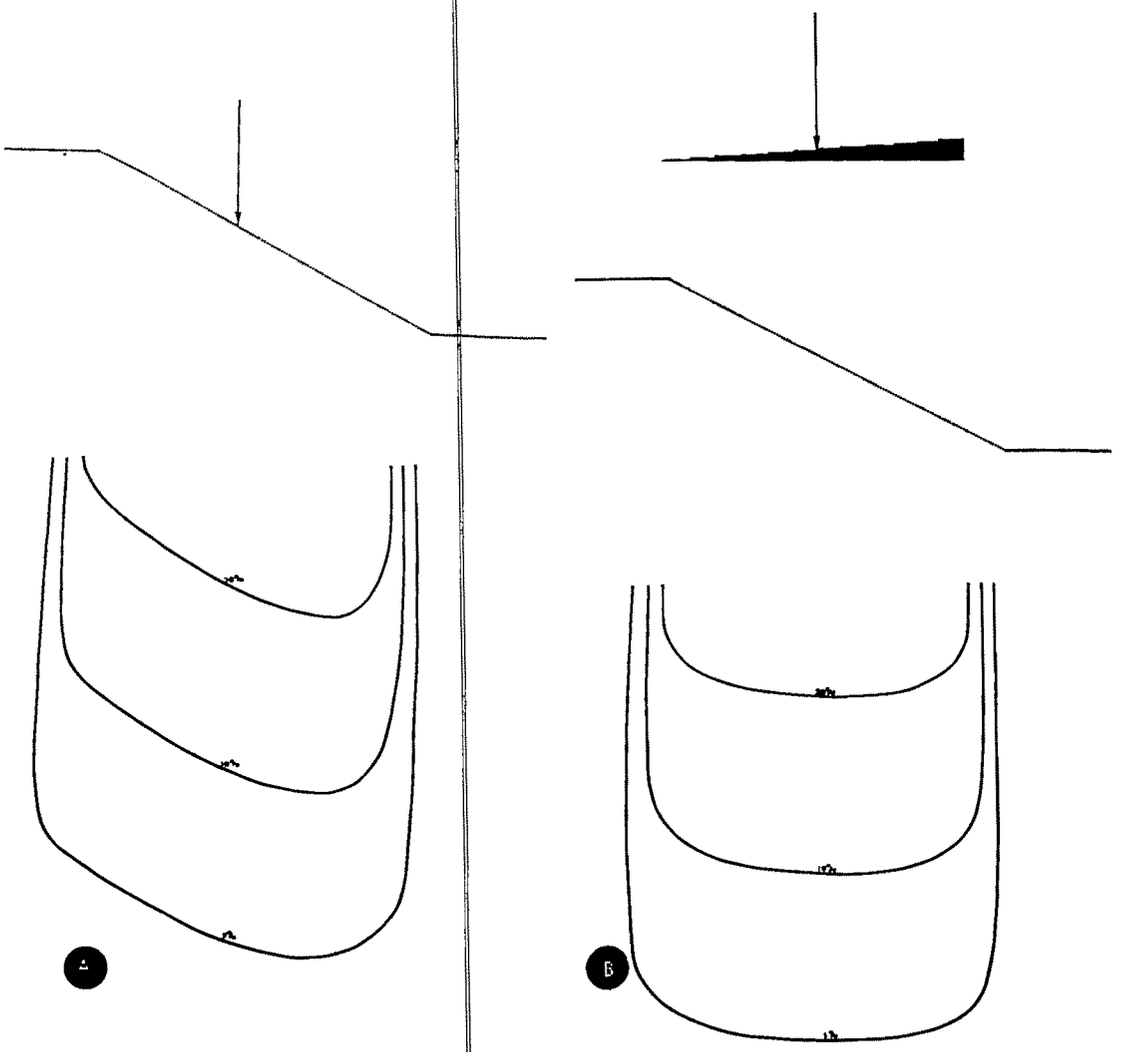


Fig. 4. (*A*) Isodose curves within a curved surface phantom without a tissue compensating filter in the beam Co^{60} teletherapy; 10×10 cm. field; 80 cm. SSD. (*B*) Isodose curves within the same phantom after inserting a tissue compensating filter in the beam. The central axis per cent depth dose at depths greater than 5 cm. is reduced approximately 1 per cent from that predicted from depth dose tables.

pensator until isodose curves within the phantom are flat across the central portion of the beam. From the resulting compensating filter, conversions between air distances and brass thicknesses can be obtained. These conversions may be used for all field sizes at a particular source skin and source compensator distance. Conversions obtained in this way are listed in Table 1 for a source skin distance of 80 cm. and a source compensator distance of 62 cm. Included for comparison are conversions calculated by dividing air distances by the density of brass.

Lateral dimensions of the blocks are less than the distance between holes in the lucite plate by an amount calculated from the expression:

$$\frac{\text{Source compensator distance}}{\text{Source lucite plate distance}} \times \text{hole spacing} = \textit{length of block side.}$$

The assembled filter is locked into place with an aluminum adapter attached to the

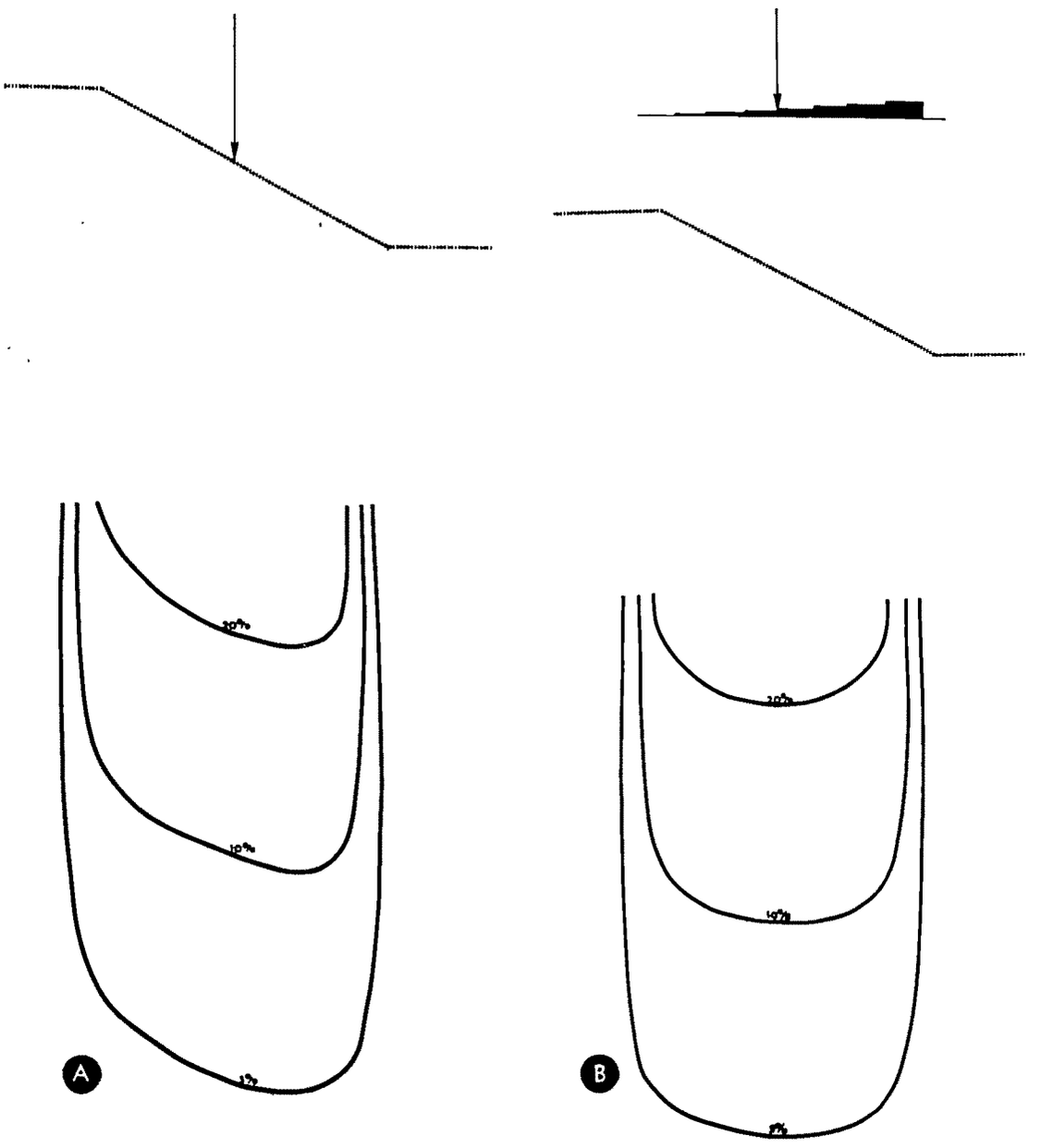


FIG. 5. (*A*) Isodose curves within a curved surface phantom without a tissue compensating filter in the beam. Co^{60} teletherapy; 15×15 cm. field, 80 cm. SSD. (*B*) Isodose curves within the same phantom after inserting a tissue compensating filter in the beam.

end of the collimator. The r/min. calibration for the field size and source skin distance selected is corrected for attenuation of Co^{60} radiation by the 2 aluminum plates in the beam when filters are used.

Filters have been assembled to compensate for a variety of irregular patient surfaces. Illustrated in Figures 2 and 3 are tissue compensating filters designed to provide flat beam entrance surfaces during treatment of carcinoma of the maxillary antrum and the esophagus.

The effectiveness of tissue compensating filters as bolus substitutes was tested by obtaining isodose curves with an isodose plotter, using water phantoms providing

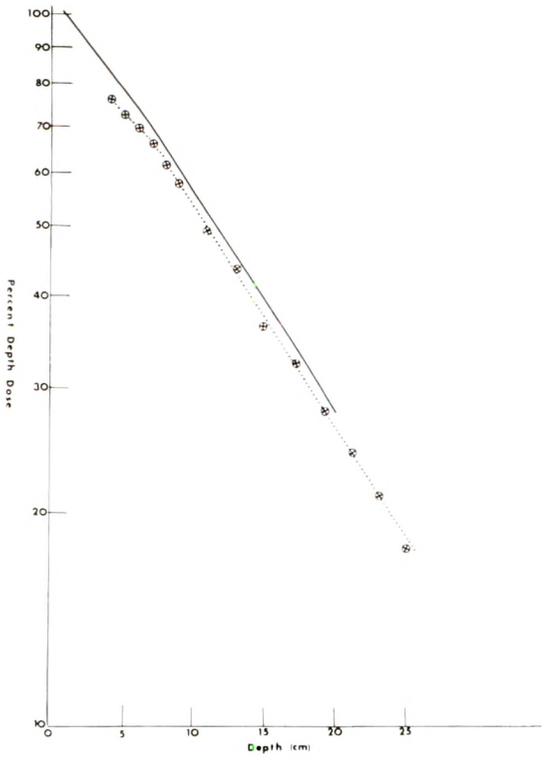


FIG. 6. Percent depth dose measured with LiF in a pressdwood phantom (dotted curve). Tissue compensating filter in beam compensates for irregular curvature of phantom surface. Co^{60} teletherapy; 10×10 cm. field, 80 cm. SSD. Solid curve taken from Table 6.3 (*Brit. J. Radiol.*, 1961, Suppl. 10, 56) describes depth dose measured with LiF in pressdwood phantom with flat beam entrance surface.

irregular beam entrance surfaces. Examples are shown in Figures 4, *A* and *B* and 5, *A* and *B* of resulting isodose distributions without and with a compensator in place. Central axis depth doses were measured with LiF within a soft tissue equivalent pressdwood phantom with an irregular beam entrance surface. The slight decrease in percent depth dose at shallow depths within the patient diminishes rapidly with increasing depth (Fig. 6). At depths of 5 cm. or more the reduction is only 1 per cent. Since high energy radiation is generally used to treat lesions at depths greater than 5 cm., this reduction in percent depth dose at shallower depths may be interpreted as a further benefit of using tissue compensating filters.

SUMMARY

A method has been devised for rapid assembly of tissue compensating filters which provide flat beam entrance surfaces while maintaining the skin sparing effect of Co^{60} radiation. Both experimental and clinical results illustrate the effectiveness of these filters as substitutes for bolus.

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COBALT 60/80 CALCURULE*

By W. P. SCOTT, M.D.
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THE *Calcurule* (Fig. 1, *A* and *B*) is a simple device that enables one to arrive rapidly at the basic technical factors involved in telecobalt 60 treatment planning. It has a one Centimeter Measuring Scale set with 0 in the center and thus it is quite easy to place the 0 over the tumor centrum and lay out adequate margins to each side of the particular diameter. Then depending upon the choice of techniques used, fixed fields or rotation, the depth dose or tumor/air ratio are read directly from the corresponding curve. The horizontal lines running through these curves designate the field sizes, ranging from 16 through 400 cm.^{2} for depths ranging from 1 through 20 cm.

For source distances other than 80 cm. another Calcurule with the desired distance is made available more easily than modifying the Calcurule with a moving part (slide and/or cursor) to accomplish the correction.

Radiotherapists usually have a favorite distance compromising output and dosimetry for most fixed fields and find it convenient to keep it the same as the distance of axis of rotation. The tumor/air ratio curves, of course, remain the same regardless of source distance. Not only does the Calcurule enhance "on the spot" treatment planning while outlining portals but also renders *accurate* calculations possible, such as interpolating field sizes. In familiarizing

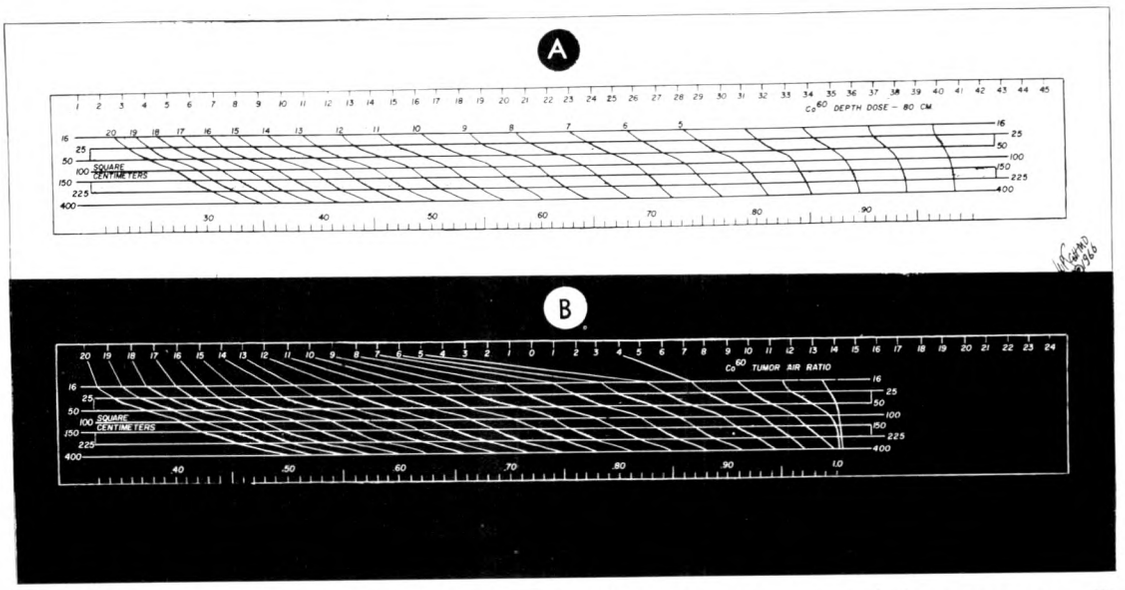


FIG. 1. (*A*) Cobalt 60 *Calcurule* showing the Centimeter Measuring Rule and depth dose percentages. To calculate the percentage depth dose at 12 cm. for a 10×10 cm. portal, follow the 12 cm. line on the scale to where it intersects the 100 square centimeter line and read .481 on the bottom scale. (*B*) The reverse side of the *Calcurule* shows the Centimeter Measuring Rule and tumor/air ratios. This side of the rule has a black background to facilitate reading under the beam localizing light in a darkened room. To estimate the tumor/air ratios at 12 cm. for a 10×10 cm. portal, follow the 12 cm. line from its point of origin on the Centimeter Measuring Rule to where it intersects the 100 square centimeter line and read .629 on the bottom scale.

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himself with the use of the device, one can grasp the fundamentals of variables in teletherapy, *e.g.*, the effect of field size, distance, depth, etc. on roentgen output far better than with tables.*

For more complex calculators,[1–4] the reader is referred to the Cobalt Rotational Therapy Calculator,† and the Cobalt (Depth Dose) Rule.‡

* The Calcurule is available through Picker X-Ray Corporation, White Plains, New York.

† Picker X-Ray Corporation, White Plains, New York.

‡ Boskamp Gerätebau K. G., Hersel, Germany.

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COMPLETE CALIBRATION OF AN X-RAY THERAPY UNIT*

By MARVIN M. D. WILLIAMS, Ph.D., ARNOLD FELDMAN, Ph.D., *and* JOSEPH A. ANDERSON, B.S.
ROCHESTER, MINNESOTA

INCOMPLETELY calibrated x-ray therapy equipment will not give a radiotherapist all of the information he needs to obtain good clinical results, regardless of his clinical ability and experience. To obtain good results he must know the volume of tissue irradiated and the exposure distribution throughout the irradiated volume; but these values will not necessarily be what he thinks they are if the calibration furnishes only the central axis exposure in air and the half value layer (HVL) for the technique used. Some treatment failures probably occur when part of a lesion does not receive as great a dose as was intended because the actual exposure distribution was not that assumed from the calibration factors. Proper dosage is extremely important in the first course of radiation therapy because it may be the only chance to obtain a good result with radiation, for radiation produces some damage to normal tissue and may change the radiosensitivity of malignant tissue.

A complete calibration of therapy equipment not only provides values for the central axis exposure rate and HVL but also gives much additional information, some of which must be checked at frequent intervals. A calibration that will enable the radiotherapist to know consistently and accurately the dose of radiation delivered is not a matter of a few hours of work once every year or so—it requires many hours of work initially and then frequent, perhaps daily, checking of many parts of the calibration. Each piece of equipment will have its own peculiarities, and when and why there may be variations in exposure will be learned if the critical calibrator constantly looks for sources of error.

This discussion of what needs to be checked or measured during the calibration of therapy equipment is based particularly on experience with orthovoltage therapy equipment, but also on some experience with superficial therapy units, cobalt 60 teletherapy units, and a linear accelerator.

TIMERS

Even electric timers are not always accurate and they need to be checked occasionally. Some timers stop the treatment before the set time is up or run beyond the set time before stopping the treatment, and some fail to stop the treatment at all. The elapsed time may be different depending on whether, in setting the timer, the index is moved just up to or is moved beyond and then back to the proper setting; the magnitude of this error is not likely to be important in the timing of treatments but may be noticeable when exposure rates are measured over short periods.

POSITION OF TUBE

Because of the protection built into x-ray tube housings, it is not possible to see the exact position of the focal spot. Since tubes may vary in length, it is conceivable that when a new tube is installed the focal spot may not be in the correct position relative to the field-defining collimator. This misalignment can cause displacement of the irradiated volume, particularly at depths in the tissue; also it may cause considerable portions of supposedly irradiated areas to be shielded by the displaced

* Presented at the Sixty-seventh Annual Meeting of the American Roentgen Ray Society, San Francisco, California, September 27–30, 1966.
From the Mayo Clinic and Mayo Foundation: Section of Biophysics.

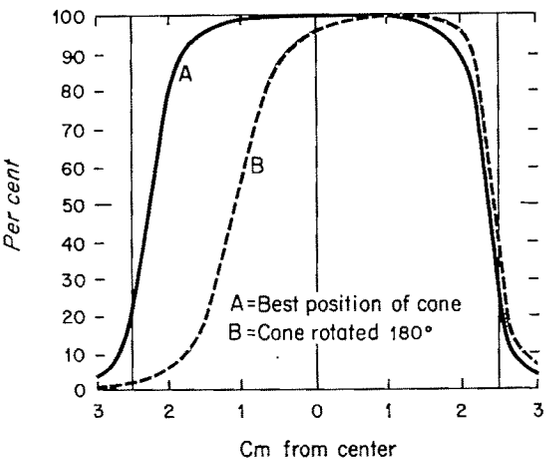


FIG. 1. Exposure rate across bottom of 5 by 5 cm. cone in two positions on the tube housing. Neither the position of lead diaphragm at top of cone nor the angle of the sides was correct. In one position these two errors tend to compensate and give a fairly good distribution, but when the cone is rotated 180° only a little more than half of the field receives an adequate exposure.

shadow of the collimator (Fig. 1). When small cones are used, particularly those that are cylindric, the exposure may be near zero over most or all of the area at the bottom of the cone.

It is possible that a tube may be rotated from its correct position when it is inserted into the tube housing, or that the holding mechanism will become loose and allow the tube to rotate. Such rotation may result in a reduced dose on one side of the field (Fig. 2); the resulting distribution of dose may be quite different from that indicated by the usual isodose charts. Tube rotations of 15° or more have been observed during checks of the calibration of equipment which was supposedly in good order. Position of the focal spot and possible rotation of the tube can be checked by a multiple pinhole camera[1] (Fig. 3).

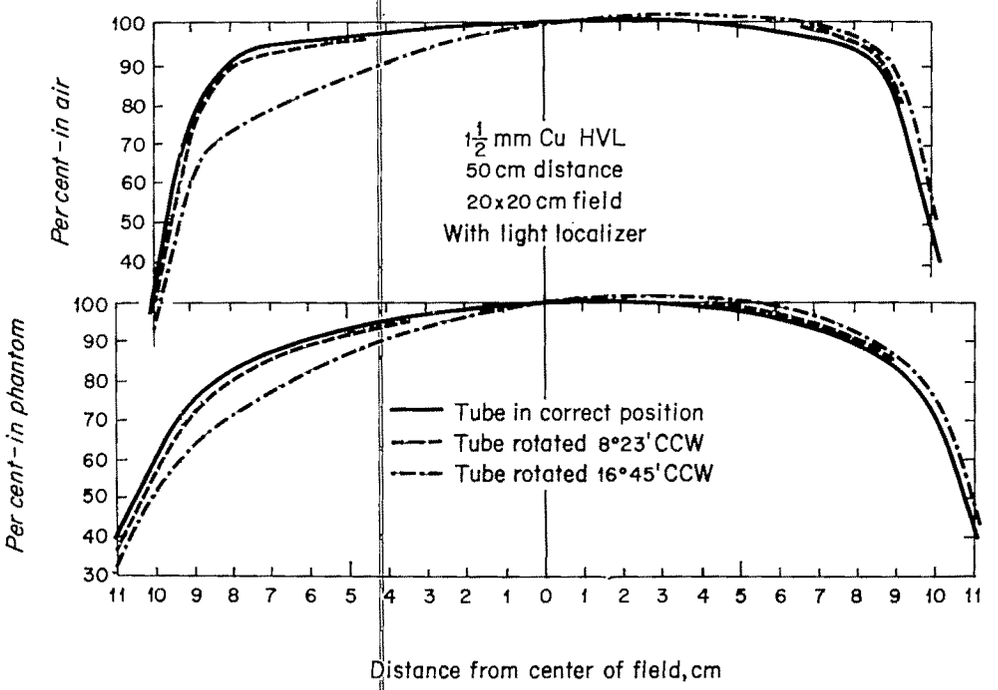


FIG. 2. Exposure distributions at right angles to tube axis in plane perpendicular to central ray when tube was positioned correctly in tube housing (*solid lines*) and when tube was rotated in respect to window in tube housing (*broken lines*). *Upper:* Distribution in air in a plane 50 cm. from target. *Lower:* Distribution at depth of 5 cm. in water phantom whose surface is 50 cm. from target. Solid lines are not symmetric on the two sides of the field because of variation in filtration through mirror in light localizer (see Fig. 6).

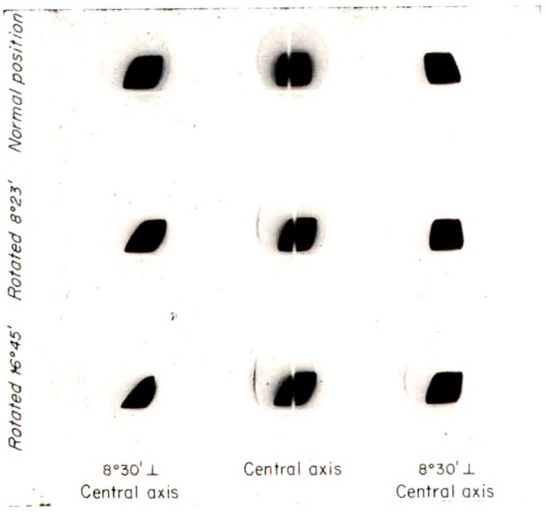


FIG. 3. Pinhole photographs of target of x-ray therapy tube in correct position in tube housing and after rotation of 8°23′ and 16°45′ in respect to window in tube housing. For each photograph, middle image is along central ray and other two are along rays 8°30′ to each side of it and at right angles to tube axis (8°30′ corresponds to 7.5 cm. from center at 50 cm. from the target). The vertical and horizontal lines do not pass through central ray but do serve as reference lines. The dark area is image of focal spot (actual size, 12 by 12 mm.) and ring around it is beryllium-covered hole in anode hood. With tube in normal position, central image of focal spot is centered in ring and sides slope symmetrically toward center. As tube is rotated, all images of focal spots move toward right side of rings, and slope of their sides rotate to right. For rotation of 8°23′, entire focal spot is just visible along left ray; for rotation of 16°45′, part of this focal spot is no longer visible and a corner of focal spot along central ray is perhaps not visible. Figure 2 shows that rotation of 8°23′ has little effect on exposure distribution, but rotation of 16°45′ produces marked reduction on left side of field.

SIZE OF FOCAL SPOT

In recent years there has been much discussion about the undesirable penumbra produced by the rather large size (diameter, 1 to 3 cm.) of cobalt 60 sources in teletherapy units, but very seldom is there mention of the penumbra produced by the large focal spots of some therapy tubes. Focal spots of therapy tubes vary from a few millimeters to more than 1.5 cm. in diameter. These variations in radiation source-size, together with variations in location of collimators from near the tube to near the skin, produce variations in the dose distribution near the edges of the fields; hence, isodose curves obtained from one piece of equipment may be unsatisfactory for use with another.

CHANGES INSIDE OF TUBES

During the operation of a tube, the focal spot area may become pitted, and tungsten may be deposited on the tube wall or on the inner surface of a hooded anode, thus effectively changing the filtration and causing a lower exposure rate and higher HVL. A decrease in exposure rate of more than 10 per cent, as a result of such changes, has been observed over an operating period of 35 hours; however, these changes may be less likely to occur in equipment manufactured in recent years.

TUBE HOUSING

On some equipment, to change the direction of the x-ray beam the x-ray tube is rotated inside a stationary metal housing.

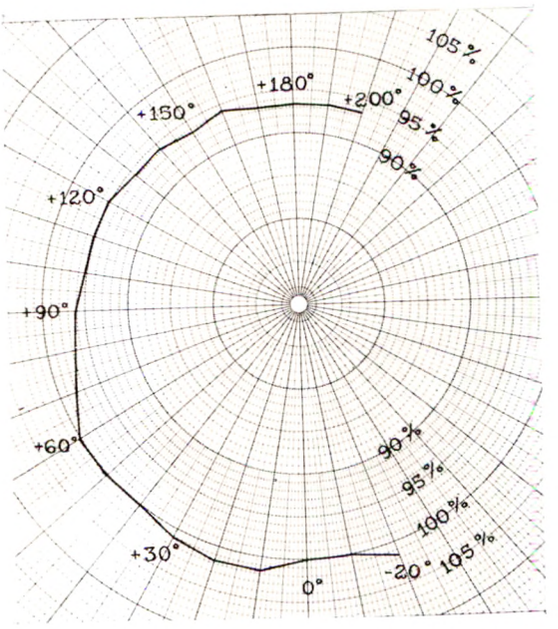


FIG. 4. Variation of exposure rate with angle of x-ray beam, caused by nonuniform thickness of metal of tube housing (tube rotates inside stationary housing). The half angle for 20 by 20 cm. field at 50 cm. source skin distance (SSD) is 11°19′.

If the thickness of the metal housing is not uniform the filtration will vary, thus causing a change in exposure rate. Figure 4 shows that the central axis exposure rate for the beam coming from such a tube housing may vary by as much as 10 per cent from its maximal value as the direction of the beam is changed. If this beam is rotated to 70° this variation in filtration will produce a difference of 3.5 per cent in the exposure rate at two edges of a 20 by 20 cm. field at 50 cm. distance.

SHUTTERS

Shutter mechanisms on some x-ray equipment and radioisotope teletherapy units open and close slowly. During these periods of opening and closing, the exposure rate may be quite different from the exposure rate when the shutter is fully open. The difference: (1) may be more noticeable near the edges of a field than at the center; (2) will be more noticeable at short distances than at long distances; (3) probably will have to be taken into account when exposure rates are being determined; and (4) may need to be taken into account when one is determining the time required to deliver a desired exposure, particularly when treatment times are short because of high exposure rates.[2,3]

FIELD-DEFINING DEVICES

Many teletherapy units have an adjustable collimator which determines the area to be treated and a light source which illuminates the area. Obviously it is essential that the light field corresponds to the radiation field. On some light localizers the light field may shift as much as a few centimeters because of a change in position of the filament in a bulb (heat may cause the filament or its support to sag) or because all bulbs do not necessarily have the filament in the same position. Correspondence of these two fields is commonly checked by exposing a film to the beam with the position of the light field indicated by lead markers. This is rather time consuming for something which may need checking every day or so. Figure 5 shows two devices which permit this check to be made very quickly after the position of the radiation field has once been determined.

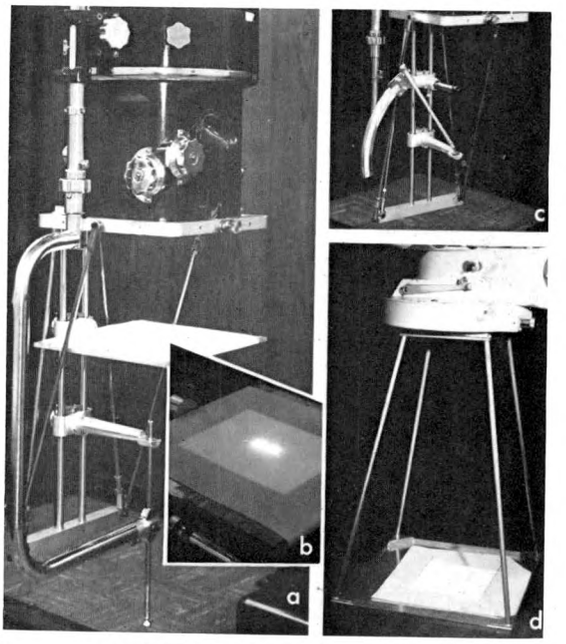


Fig. 5. Useful devices for checking equipment. (*a*, *b*, and *c*) "Checking frame" attached to the collimator of a cobalt 60 unit. (*a*) Metal plate is covered with graph paper for checking position and size of light field and distance indicated by distance lights. Below metal plate is arm, with hole near its outer end, being used for checking adjustment of back-pointer. (*b*) Another view of plate, showing light field and images of filaments of lamps used as distance indicator. (*c*) Metal plate replaced by holder for ionization chamber; arm in lower holder has needle in hole at outer end and is being used for checking adjustment of pin-and-arc. (*d*) Frame which attaches to light localizer on x-ray unit. It is being used to verify that position of light field coincides with rectangle that indicates position of radiation field.

In many of these light localizers there is a mirror in the radiation beam, at an angle of 45° to the central ray, which reflects the light from a lamp to the treatment area. The length of the path of the radiation through the mirror varies from one edge to the other. In one localizer the actual path lengths at the edges were 84 per cent and 128 per cent of the length at the center of the beam for a 20 by 20 cm. field at 50

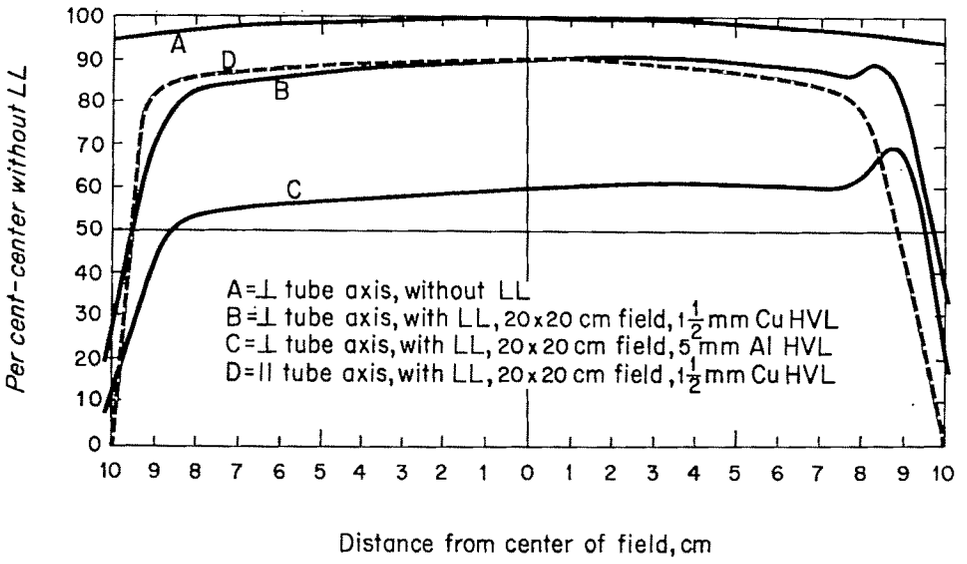


Fig. 6. Exposure distributions in air in plane perpendicular to central ray at 50 cm. from target. Curves, A, B, and C represent distributions at right angles to tube axis; A is without light localizer and is symmetric; B and C, with light localizer in place and adjusted to give a 20 by 20 cm. field, are not symmetric because path length of radiation through 45° mirror in localizer is 28 per cent greater at lower edge of the mirror (left) and 16 per cent less at upper edge of mirror (right) than through center. Humps on right side of B and C are due to radiation that passes by upper edge of mirror. The central ray exposure rate through light localizer for radiation with a HVL of 1.5 mm. Cu is 90 per cent and for 5 mm. Al, 60 per cent of exposure rate without light localizer. Curve D represents exposure distribution parallel to tube axis for same conditions as for B; the cathode of the tube was to the right.

cm. distance. Figure 6 shows that the mirror reduces the exposure rate at the center of the field by 10 per cent for a beam with a HVL of 1.5 mm. Cu and by 40 per cent for a beam with a HVL of 5 mm. Al. For these two beams the mirror reduces the exposure rates near two edges of a 20 by 20 cm. field by 13 and 8 per cent and by 48 and 35 per cent. It is evident that the use of the light localizer markedly reduces the central axis exposure rate, slightly increases the HVL, and delivers a smaller dose to one side of treatment fields.

Under the discussion of the position of a tube in the tube housing, it was mentioned that, if the focal spot is not properly positioned above the center of the collimator, part of the area supposedly being treated may receive very little radiation, particularly with small, cylindric cones. It is also necessary that the sides of cones be at the proper angle with respect to the base of the cone. Figure 1 illustrates the reduction in the area supposedly exposed to radiation which may occur due to a poorly constructed cone. Both the angle of the sides and the position of the collimating diaphragm of this cone were incorrect; in one position the two errors fairly well cancelled but in other positions the exposure distribution was unacceptable.

A large number of cones have been found to have unacceptable exposure distributions. The difference between the exposure rate near the edge of a field and that at the center will generally be greater at depths within the body than in air at the source skin distance (SSD). It would be desirable to have a somewhat greater air exposure rate at the edge of a field so that the dose at a depth would be nearly uniform in planes perpendicular to the central ray. With presently available equipment the exposure rates near the edges of fields frequently are less than 80 per cent of the rate at the center.

Checking the exposure rate distribution over the field area of all of the commonly

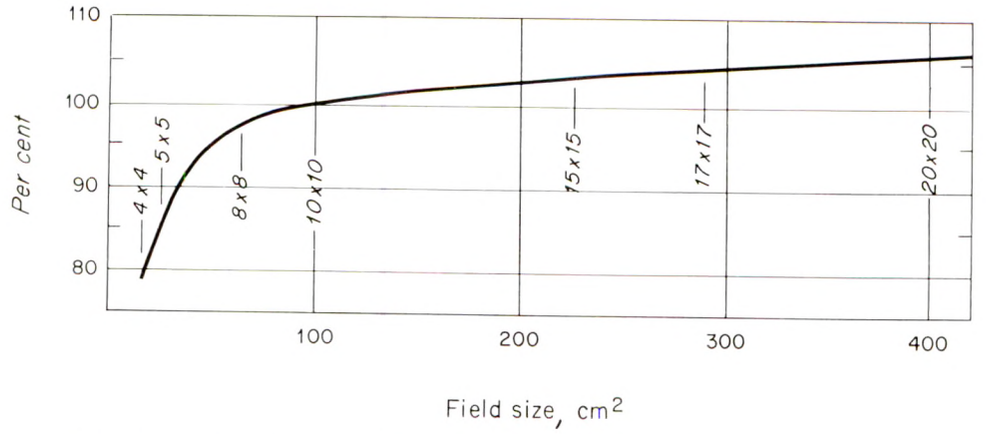


Fig. 7. Variation of exposure rate with size of square fields on a cobalt 60 teletherapy unit, with the exposure rate for a 10 by 10 cm. field as 100 per cent.

used field sizes with a condenser r meter is a tedious procedure. A more satisfactory method is to use a ratemeter with an ionization chamber whose position in the radiation field can be remotely controlled. One common method of checking the distribution is by exposing a film. The use of film for this purpose is subject to many errors because film density depends on several factors in addition to quantity of radiation. Also, since the r per minute from therapy equipment is high, short exposures are required in order that the film density will be in the range in which variations in radiation exposure can be detected. Short exposure times may result in an appreciable variation in radiation exposure because the film may not be uniformly exposed as the shutter opens; this nonuniform exposure could be mistaken for a variation in exposure rate during normal operation of the equipment.

Some therapy units have cones and collimators for which the central axis air exposure rates are independent of field size, but generally this is not true. Figure 7 shows the variation of air exposure rate with field size for a cobalt 60 teletherapy unit, a variation that is too large to be ignored. Such an amount of variation is not unusual for x-ray or radioisotope teletherapy units, yet many calibrations do not include these data.

DISTANCE

Variations of 1 cm. or more in the length of the cone and in various distance measuring devices have been found frequently. A variation of 1 cm. in a SSD of 50 cm. changes the exposure rate by 4 per cent and, although this is rather a small error, a correction should and easily can be made for it.

Some distance measuring devices make use of the images of the filaments of a light bulb or of slits of light. These may change position because of sagging of the filament in the bulb or because the position of the filament is not the same inside all bulbs; it may be desirable to check the adjustment of such devices as often as every day. Figure 5 shows equipment which permits the adjustment of such a light device to be checked easily and quickly; with such equipment available, it is more likely that frequent checks will be made.

BACK POINTERS AND PIN-AND-ARCS

Mechanical devices used to aim a beam in the desired direction or to position the patient, such as back pointers and pin-and-arcs, may get out of adjustment because of the loosening of set screws or because of being dropped, hit, or handled roughly. If they are not properly adjusted their use will not aim the beam in the desired direction. Such devices may need to be checked

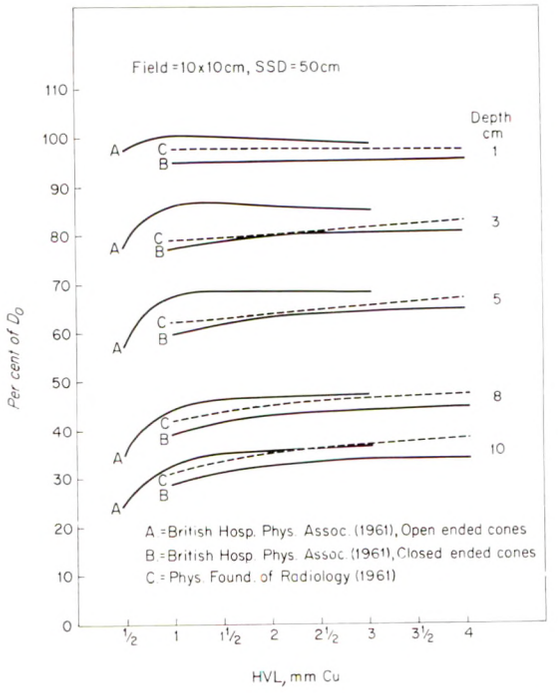


FIG. 8. Comparison of depth dose data from two sources[3,6] for various qualities of radiation at several depths. If these data were normalized for a depth of 5 cm. instead of for the surface, curves A and B would differ by less than 1 per cent for nearly all points except for those at 1 cm. depth; the percentage difference between curves B and C would be less than in this graph, but would still be appreciable.

frequently. Equipment, as shown in Figure 5, which permits quick, easy, and accurate adjustment makes it much more probable that checking and necessary adjustments will be done frequently.

DEPTH-DOSE TABLES AND ISODOSE CHARTS

There are considerable differences in the many central axis depth dose tables and isodose charts available in books and from other sources (Fig. 8). These differences do not necessarily indicate that any of the data are wrong, but they do show that differences in source size and position, arrangement of diaphragms, use of cones with or without bottoms, presence of mirrors in the beam, and other variables may cause variations in central axis depth dose values and in the shape of isodose curves.[4] Before a decision is made to use any particular set of tables or charts, a number of spot checks should be made to determine whether or not the values are correct for the equipment being used. Replacement of the x-ray tube or radioisotope teletherapy source may change depth dose values and the shape of isodose curves.

OTHER FACTORS

A number of factors which have been found to affect the exposure from teletherapy sources, the volume of tissue irradiated, and the exposure distribution throughout the volume have thus far been discussed briefly. Many other factors, such as changes in sensitivity of milliampere and volt meters, inaccurate calibration of r meters, and improper methods of using r meters, also could have been discussed.[7] Some of these same factors and others also affect the calculation of dose from exposure.[8] Some of the factors that have been discussed will not apply to all equipment; each piece of equipment will have its own peculiarities. It is not possible to predict all that should be included in a complete calibration of a specific piece of equipment, but additions to the list will be made by an alert physicist or therapist.

There are many factors in radiation therapy that cannot be known accurately, are not known accurately now, or cannot be controlled, such as exact size, extent, and radiosensitivity of a lesion and the exact effect on the exposure, quality of radiation, and dose distribution produced by various kinds of tissue in the path of the radiation. Hence, it is desirable to control as well as possible those factors that can be controlled.

Often the clinical results obtained with high energy equipment—million volt x-ray equipment, cobalt 60 sources, betatrons, and linear accelerators—have appeared to be superior to those obtained with the older and more commonly used orthovoltage equipment. In part this may be because the first use of many high energy

sources of radiation commonly was in an institution where fulltime radiation therapists, radiation physicists, and, often, radiobiologists were available. Before patients were treated, the physical characteristics of the equipment were thoroughly studied, and frequently some biologic evaluations of the radiation were made. The plans for treating the first patients were carefully worked out and great care was exercised to be sure that the amount of radiation given and its distribution were known as accurately as possible.

May not the commonly assumed superiority of high energy teletherapy equipment be due, at least in part, to the fact that the equipment has been very thoroughly calibrated, which enables the radiation therapist to deliver the dose he intends? As such high energy equipment becomes more widely used, is there not a probability that the calibrations will often be less thorough, just as they often have been for orthovoltage equipment? And might not this cause the doses to be different (generally less) than the radiation therapist intends, and the clinical results perhaps to be no better, or even worse, than those previously obtained with orthovoltage radiation?

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This material has been accumulated over a period of many years. It is a pleasure to acknowledge the contributions made by two former associates, Bernice Borrman Palos, now of Los Altos, California, and Ann L. Forsaith, now of Royal Oak, Michigan.

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FAST NEUTRON BEAM RADIOTHERAPY*

STATUS AND PROSPECTS

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THE potential value of fast neutron beams for human cancer radiotherapy is dependent upon their penetration in tissue relative to cobalt 60 gamma rays and high energy x-rays, their oxygen effect ratio, their fractionation effects, their technologic feasibility, and their cost. Some of these radiobiologic and technologic aspects have been resolved by investigations currently reported; some are in the process of being resolved; and others require additional investigation. In this "Status and Prospects Report" the status of these radiobiologic and technologic aspects is reviewed and several independent findings with respect to prospects for fast neutron beam radiotherapy are described. Certain theoretic radiobiologic and clinical considerations governing the re-introduction of fast neutron beam irradiation into human cancer radiotherapy practice have already been the subject of an extensive review[1] and the basic requirements for the clinical application of a 14 mev. monoenergetic fast neutron beam* have been developed.[2] A single trial of cyclotron-produced fast neutron beam† human cancer radiotherapy has been reported with an adverse judgment as to its effectiveness and safety,[26] and this judgment has been reaffirmed.[27] There is no evidence, and, indeed, there cannot be, until fast neutron beam human cancer radiotherapy is restudied, that this judgment is invalid. Certain aspects of the human response are again under study with a cyclotron-produced fast neutron beam[19] and the development of a 14 mev. fast neutron beam appropriate for human cancer radiotherapy would appear to be technologically feasible.[this communication, 10,28]

Recent communications define, by measurement in tissue equivalent materials, the penetration of cyclotron-produced fast neutrons as having depth dose characteristics somewhat inferior to those of 250 kv. x-rays[21] and of 14 mev. fast neutrons as somewhat superior to cobalt 60 gamma rays.[13,15,22] Slight subsurface ionization build-up, similar to but less than that associated with cobalt 60 gamma rays, was found with both neutron beams.

Quantitative mammalian cell radiobiologic studies indicate that the oxygen effect ratio (sometimes called by other authors the oxygen enhancement ratio, abbreviated, OER) is an inverse function of the logarithm of mean linear energy transfer (LET) with limiting values of the ratio of near 3 at low and of near 1 at high values of LET.[1] The few quantitative mammalian cell radiobiologic studies which have been performed suggest that the oxygen effect ratio for cyclotron-produced fast neutrons[8] is the same as that for 14 mev. fast neutrons,[3,4,12,13] and that this ratio has a value of about 1.7. There would not appear, therefore, to be any radiobiologic advantage due to the oxygen effect in the use of one or the other of these two neutron beams.

The cellular radiobiology of low LET (cobalt 60 gamma rays and high energy x-rays) dose fractionation effects on organized tissues is under active study at present[11]

* 14 mev. monoenergetic fast neutrons produced by the D–T reaction.

† Range of energies, 0–19 mev.; mean energy, 6 mev. fast neutron beam produced by the D–Be reaction.

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and a few studies have been performed with the higher LET cyclotron-produced fast neutrons (see below). At higher values of LET than those mean values obtaining in the case of either the cyclotron-produced or the 14 mev. fast neutrons, fractionated doses are fully cumulative. It is to be inferred that fractionated doses of either of these fast neutron irradiations would be more fully cumulative than similarly fractionated doses of cobalt 60 gamma rays or high energy x-rays. Different radiobiologic experiments performed by the same investigators have yielded, however, contradictory results. Survival curve studies of a mouse tetraploid ascites tumor showed no difference in the degree of recovery after paired doses of either x-rays or cyclotron-produced neutrons.[16] The same investigators demonstrated that the 4 day mortality dose for mice (interpreted as being due to depletion of the epithelial cells lining the small intestine) was not different for cyclotron-produced neutron irradiation when administered either as two equal fractions separated by 4 to 6 hours or as a single irradiation with the same total dose, while under similar fractionation conditions with 250 kv. x-rays, the total x-ray dose had to be increased by 30 per cent to induce the same mortality rate when this dose was administered in two fractions separated by 6 hours.[17] In addition, the RBE of neutrons compared with x-rays was found, in these experiments, to be greater with small doses.* The most suggestive findings bearing upon this aspect of fast neutron beam irradiation are those resulting from the clinical studies recently reported[19,20] which showed a somewhat greater relative biologic effectiveness (RBE) for certain human skin effects of cyclotron-produced fast neutrons, as compared with high energy x-rays, for fractionated than for single doses.† Fractionation studies have shown no qualitative effects on the cell population kinetics of normal mouse skin due to LET characteristics of either cyclotron-produced fast neutrons, 15 mev. electrons, or 250 kv. x-rays.[14] These studies did suggest, in accordance with the considerations developed above and in the first footnote, a modification of the fast neutron RBE when the dose was fractionated.

The RBE of both cyclotron-produced and 14 mev. monoenergetic fast neutron beams does not vary with the depth of penetration of such beams in tissue-equivalent materials. This has been studied using mammalian cells in culture as the biologic test material.[5,6]

While the experimental study of radiation dose, cell survival curves has resulted in a vastly increased understanding of certain features of human cancer radiotherapy, such study has generally been of single systems, only. The human condition is, however, a systems complex of many components which both respond to irradiation at different rates and interact. Experimental radiobiologic models for the study of such systems complexes are being developed,[11,23,24]‡ but, until such time as definitive studies bearing on the neutron fractionation problem can be performed with these models, painstaking studies of the human patient, such as cited above, must provide the working bases for the reassessment of fast neutron beam human cancer radiotherapy.

The technologic feasibility of cyclotron-

* Consideration of the relationship of two mammalian cell survival curves of different shapes, one being exponential and the other being sigmoid (as is found with, respectively, high and low LET radiations), will show that dose ratios (RBE's) for equal cell survival are greater at small than at large doses. The implications of this characteristic for small dose, fractionated and protracted human cancer radiotherapy with fast neutron beams remain to be investigated.

† The mean RBE ratios (neutrons/x-rays) determined for the human skin studies were 2.9 for single doses (340 rads, neutrons) and 4.3 for fractionated doses (1 patient, 6×100 rads in 3 weeks).[13] During a recent visit, one of the authors (JRA) saw a patient who had been irradiated over several test sites on each thigh with small doses of both 8 mev. x-rays (maximum dose at the surface by the introduction of absorbers) and the cyclotron-produced fast neutrons to biologically equivalent doses. Slight pigmentation persisted at all sites but there was no increase of injury with time. The research group is now performing matching x-ray (8 mev.) and fast neutron beam irradiations in 12 fractions, twice weekly, to total x-ray doses of 3,000 rads with the fast neutron dose less by a factor, presumably generous but made deliberately so because of the apparently greater RBE with fractionation, of five.[20]

‡ Radiation effect studies are being planned for the two-component systems described in Reference.[24]

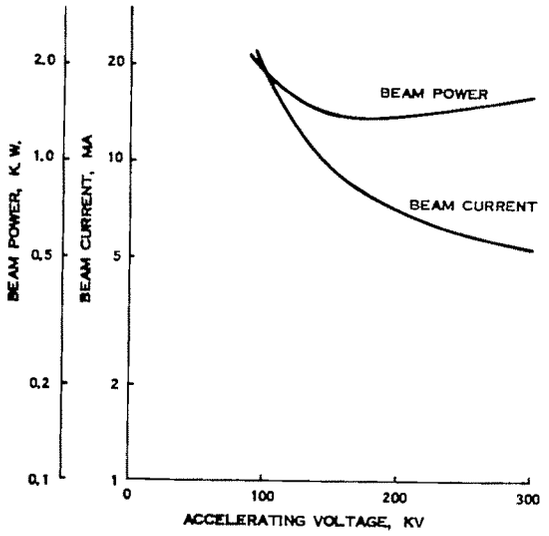


FIG. 1. Beam current and power necessary to produce 10^{12} neutrons/sec. using deuteron beam on 4 curie/in.^{2} titanium tritide target.

produced fast neutron beam human cancer radiotherapy is already established. In order for 14 mev. fast neutron beam radiotherapy to be practical, certain performance requirements have to be met. These are a clinically useful dose rate at a distance permitting optimal collimation and shielding and a neutron source of acceptable diameter. This dose rate must be greater than, say, 10 rad/min. at the irradiated subject (with an RBE of, say, 3; this is biologically equivalent to 30 rad/min. high energy x-rays). Applying a conversion factor of 1.6×10^8 neutrons/cm.^{2} = 1 rad, it can be shown that a neutron generator producing 10^{12} neutrons/sec. in an isotropic distribution will deliver a dose rate of 12 rad/min. at a distance of 50 cm. Therefore, it is of interest to examine the possibilities for producing neutrons at the rate of 10^{12} per second and obtaining adequate collimation and shielding at a distance of 50 cm.

The reaction of accelerated deuterons with tritium (the T(d,n)He^4 reaction) is by far the most useful means of producing 14 mev. neutrons. The most common means of utilizing this reaction are either to accelerate a beam of deuterium ions into a target containing tritium or to accelerate a mixed beam of deuterium ions and tritium ions into a target containing the same deuterium-tritium mixture. In either case, only low acceleration energies of the order of a few hundred kv. are required to produce the D-T reaction yielding 14 mev. monoenergetic neutrons.

The beam current required to produce 10^{12} neutrons/sec. by accelerating deuterium ions into a target containing 4 curies/in.^{2} of tritium is shown in Figure 1. The corresponding power dissipation also is shown in Figure 1.

A good design criterion is to choose an accelerating energy corresponding with the minimum power requirement. In this case, an operating voltage of 200 kv., which is towards the high voltage end of the minimum of the power curve, is attractive in order to achieve better target life. The required current at this voltage is seen to be 7 ma. However, an operating current of 10 ma. will be chosen here in order to provide an average neutron output of 10^{12} neutrons/sec. over one half life of the tar-

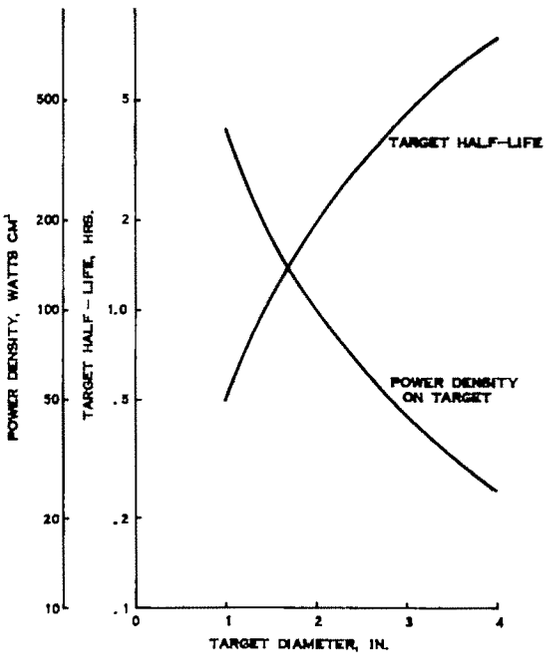


FIG. 2. Target half life and power density of neutron generator using 10 ma., 200 kv. deuteron beam on 4 curie/in.^{2} titanium tritide target.

get. An accelerator operating at 10 ma. and 200 kv. is well within the capabilities of present technology.

A major limitation on the use of neutron generators of this type is the lifetime of the tritium-containing target. Accumulated experience in many installations indicates that target half lives of approximately

$$1 \frac{\text{ma.-hr.}}{\text{cm.}^2}$$

may be expected. Using this number, the target half life may be determined as a function of target diameter, as shown in Figure 2. It is seen that reasonable target lifetimes are only approached when using the larger diameter targets. The large target diameter is disadvantageous for shielding purposes, however, as will be discussed later. It should also be mentioned that the target lifetimes can be extended by a factor of from 10 to 30 by the use of a rotating target assembly which effectively increases the target area by this factor. Such assemblies have a serious disadvantage for the present application in that they introduce a large bulk in the vicinity of the target which may interfere with collimator design. It is concluded, therefore, that the clinical usefulness of generators, using this approach, will be limited by their short target lives.

Using the alternate approach of a mixed deuterium-tritium beam, the required

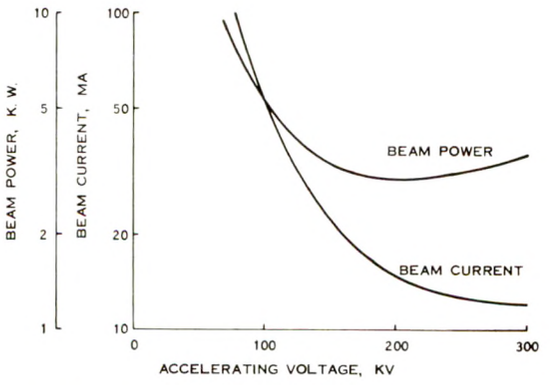


Fig. 3. Beam current and power to produce 10^{12} neutrons/sec. using 50 per cent deuteron–50 per cent triton beam on titanium supported target.

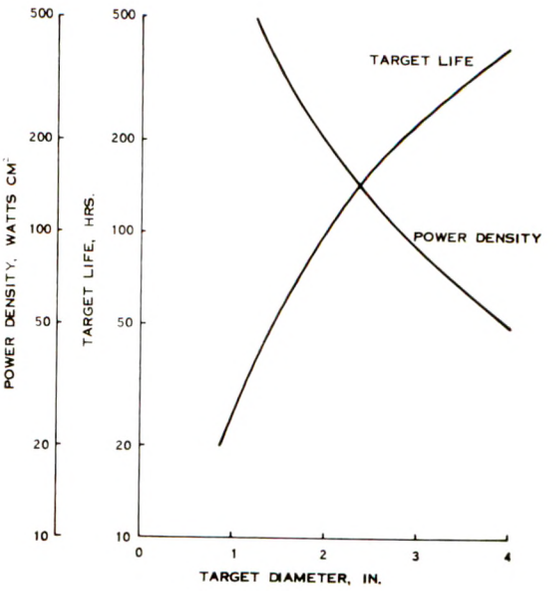


Fig. 4. Target life and power density of neutron generator using 20 ma., 200 kv. beam of 50 per cent deuterium–50 per cent tritium for 10^{12} neutrons/sec. output.

beam current is more than a factor of 2 greater, as shown in Figure 3. It is seen that, at the operating voltage of 200 kv. a beam current of 20 ma. is required, using conservative design criteria. Using this approach, however, the target life is limited only by sputtering, or mechanical erosion, of the target material, rather than by removal of the tritium. In this case, target lifetimes of

$$100 \frac{\text{ma.-hr.}}{\text{cm.}^2}$$

can be expected. The target life and power density are shown in Figure 4 as functions of target diameter. It is seen that adquate target life is realized even with the smaller targets, but that the power dissipation problem becomes severe at the lower target diameters. A suitable target diameter would appear to be 2 inches, which should give a life of approximately 100 hours and a power density of approximately 200 watts/cm.^{2}. Such a generator is well within the capabilities of present technology and the target life is sufficient for it to be clinically useful.

Another important consideration in neutron generator design is the rate of tritium usage. This is important not only because of the high cost of tritium but also because of the radiation hazard associated with handling large quantities of this material. Considering, for the moment, differentially pumped accelerators, it is seen that by using the mixed deuterium-tritium beam, all the tritium used must end up in the vacuum pump. With the deuterium beam and tritium target, somewhat less than half the tritium used is driven into the vacuum and hence ends up in the pump, with the remainder being disposed of along with the used target. At the present time, ion sources of the Duoplasmatron type are capable of delivering ion beams of 20 ma. with a gas utilization efficiency of approximately 80 per cent. Using the mixed beam approach with such a source, the rate of use of tritium would be 28 curies/hr. The corresponding rate using 4 curies/in.^{2} tritium targets would be approximately 6 curies/hr. This difference is largely offset, however, by the facts that the area of tritium target must actually be larger than the portion used and that the tritium in the form of a target is much more expensive than in gaseous form.

A much more desirable form of neutron generator for the present application would be the uniform-pressure sealed tube. This type of generator contains the deuterium-tritium mixture at a uniform pressure throughout the tube and the gas is continuously reused rather than being pumped away. For this reason, the rate of tritium usage is an order of magnitude less than with either of the above differentially pumped generators. Unfortunately, the highest output presently obtainable with a constant pressure tube is 10^{11} neutrons/sec. with the required 10^{12} neutrons/sec. appearing to be somewhat in the future.

In the design of a neutron collimator for radiotherapy, a useful criterion appears to be that the dose rate should be a factor of 20 less outside the beam than in the beam. This factor is stated in the National Bureau of Standards Handbook No. 76 as a minimum for x-ray radiotherapy. It is desirable to use the minimum adequate shielding thickness, consistent with the protection of the patient, in order to obtain the highest neutron output. Further, the dose rate at the edge of the beam due to scattered neutrons will be of the order of a few per cent of that in the beam and additional shielding would have little effect on the dose rate near the edge of the beam.

The attenuation of neutrons on passage through matter is usually found to follow an exponential law:

$$I = I_o e^{-x/\lambda} \qquad (1)$$

where I_o and I are the initial and final intensities, respectively, χ is the thickness traversed, and λ is a parameter characteristic of the material which may be called a relaxation length. The intensity of neutrons still possessing their initial energy always follows a law of this form. However, the material will usually have a different collision cross section for the lower energy neutrons that have already undergone one or more collisions so that the *dose rate* may have a different form from Equation (1). An example of this are most heavy metals which have a high inelastic scattering cross section, and hence a high initial attenuation of 14 mev. neutrons, but which are very ineffective in removing the low energy neutrons. When using a shield containing such a metal (iron, for example), it is, therefore, imperative that sufficient hydrogenous material be included to attenuate the neutrons after their energy has been decreased.

From Equation (1), it is seen that a thickness of 3 relaxation lengths of a material will decrease the neutron flux by the required factor of 20. However, in applying this fact, care must be taken that the relaxation length used is with respect to dosage and not merely degradation of the 14 mev. neutron flux. Iron is a promising material for collimator construction because of its large cross section for nonelastic scattering in which the energy of a

14 mev. neutron is reduced to below 1 mev. in a single collision. The relaxation length with respect to this process is approximately 8.5 cm. so that 95 per cent of the 14 mev. neutrons will be removed by 26 cm. of iron. Most of these neutrons have not been absorbed, however, but have merely had their energies reduced to somewhat below 1 mev. At this energy, these neutrons are still capable of delivering surface dose rates nearly as high as 14 mev. neutrons. Furthermore, these lower energy neutrons have very long relaxation lengths in iron and must be removed by a better neutron absorber, such as a hydrogenous material. For this reason, neutron shielding measurements conducted using a detector having a threshold in the region of a fraction of 1 mev. can be misleading and should be interpreted with care. These low-energy neutrons now have a relaxation rate with respect to dosage of approximately 5 cm. in polyethylene so that an additional 15 cm. of this material should yield the required dosage attenuation. Therefore, it is seen that the required shielding can be obtained with a thickness of less than 50 cm. by the use of suitable composite shielding materials.

In the design of a neutron collimator, however, it must be observed that the above consideration applies only in the case of a neutron generator having a target which is small compared with the area being irradiated. This can best be illustrated by means of an example such as that shown in Figure 5. In this example, a neutron generator having a target diameter of 3 inches is used to irradiate an area of the same diameter. In this case, neutrons from half the target area can reach a point 3 inches outside the treatment area by traversing two or less relaxation lengths of the shielding material. Thus, the neutron flux reaching this point would be attenuated by a factor of less than $2\epsilon^{-2} \doteq 15$ so that the dosage would be more than 30 per cent above the acceptable maximum. Therefore, if neutron generators having large targets are to be employed, it will be necessary to compensate by using thicker shielding. In the ideal case of a point source of neutrons, this effect would be negligible.

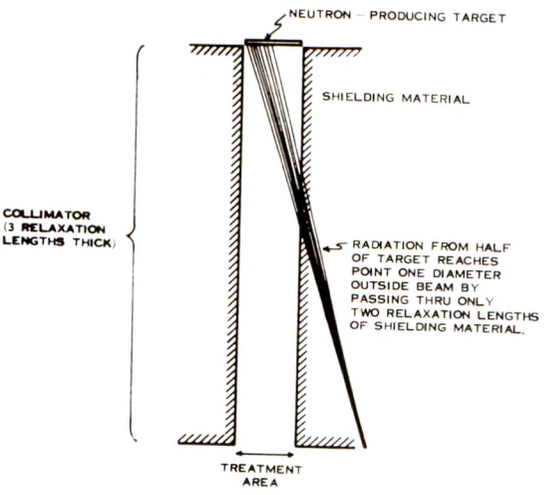


Fig. 5. Difficulty of collimating beam from neutron producing target of large diameter.

While the capacity to perform a scientific biomedical study is not necessarily dependent upon financial means, the introduction of the results of such a study into clinical practice frequently is. The cost of a 14 mev. monoenergetic fast neutron beam generating and related equipment appropriate for radiotherapy cannot be determined at this time. Certainly, the research and development costs to establish its technologic feasibility will be great and it is not to be expected that they would be recovered from such clinical applications as might result. The cost of a cyclotron-produced fast neutron beam generating and related equipment can be determined and, certainly, it is greater by an order, or more, of magnitude than the cost of the positive ion accelerating devices required to produce 14 mev. neutrons.

Other methods for the production of fast neutron beams are under active study by industry. One such method is the generation of cyclotron-produced fast neutrons with energies greater than 10 mev. by the $Be^{9}(He^{3}, n)C^{11}$ reaction which is induced by He^{3} particles accelerated to energies of

20 mev.[18] Fast neutrons may also be produced by the energy transfer processes which occur in the absorption of very high energy electron and photon beams[25] and methods for producing fast neutron beams through the intermediary of very high energy electron accelerators are being studied.[9]

CONCLUSION

There are radiobiologic reasons, which have been discussed, for studying the clinical applicability of fast neutron beam human cancer radiotherapy. The spatial requirements of dose distribution for human cancer radiotherapy can be met by a 14 mev. monoenergetic fast neutron beam. It has been shown that adequate collimation can be achieved in a 50 cm. length and that at this distance a generator producing 10^{12} neutrons/sec. will deliver a clinically useful dose rate at the patient. It has also been shown that such a generator having a target life of approximately 100 hours can be constructed using existing technology.

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ST. AGATHA AND INADEQUATE SIMPLE MASTECTOMY*

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DR. EDWARD F. LEWISON,[3] in his book on breast cancer, has told well the story of St. Agatha, the Patron Saint of Breast Disease. St. Agatha was born on the island of Sicily in the third century A.D. She came from a family of nobility and was described as a woman of great beauty. Quintianus, the Governor of Sicily, and a persecutor of the Christians, attempted to seduce St. Agatha but she spurned his attentions. Quintianus, in reprisal, imprisoned her in the brothel of Aphrodesia. After a month of captivity, St. Agatha was once again brought before Quintianus, but she continued to resist.

The most authentic version of St. Agatha's torture relates that Quintianus ordered St. Agatha to be bound to a pillar and that her breasts be torn off with iron shears.

She was cast into a dungeon to die, but the Lord sent St. Peter to restore her breasts. When Quintianus learned of the miracle, he ordered St. Agatha to be burned alive.

As soon as she was placed upon the blazing pyre an earthquake shook the city and the people demanded her immediate release. She was returned to prison where she prayed for death.

Another version states that St. Agatha was put upon a rack, hot iron plates were applied to her flesh and her breasts were cut off. That same night she was visited by St. Peter who restored her breasts.

A short time later the city suffered a severe earthquake and the people were so overwrought that Quintianus anticipated an uprising unless St. Agatha was freed. St. Agatha prayed to die and on February 5th she was buried with great reverence.

About 1 year after her death, the city was threatened by an eruption from Mount Aetna. The citizenry went to St. Agatha's tomb for shelter. They took the veil of St. Agatha, placed it on a lance and marched to meet the molten lava. The city was spared when the lava swerved to another direction. Those who observed this miracle paid homage to St. Agatha and were converted to Christianity.

St. Agatha's name is in the Litany of the Saints and in the Canon of the Mass. She is both a saint and a martyr. Fortunatus, in the sixth centruy, mentions her as one of the celebrated Christian virgins and martyrs. The Bible's Song of Solomon is said to have predicted the martyrdom of St. Agatha. She is the Patron Saint of the island of Malta and of the cities of Catania and Messina. Her assistance is sought by many who have breast disease since she has become the Patron Saint of the Breast and Wet Nurses.

Pictorially, she is shown as carrying her breasts on a salver and these have been misinterpreted as loaves of bread. Accordingly, the custom arose of blessing bread on St. Agatha's Day. In Scandinavia it is thought that St. Agatha was brushed to death; therefore, it has become traditional on February 5th for girls to abstain from brushing their hair.

The preceding is by way of introduction to the topic of inadequate simple mastectomy. Recently, there has been considerable discussion about simple mastectomy *versus* radical mastectomy in the treatment of breast cancer. This report will not attempt to compare the merits of each technique.

Simple mastectomy is being used as a treatment for benign lesions such as chronic cystic mastitis, persistent sanguineous nipple discharge, benign cystosarcoma phyl-

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loides and mammary hypertrophy. Although "simple mastectomy" suggests total removal of breast tissue, the appearance of the operative site indicates that, at times, only a wide local excision has been done or protuberant breast tissue has been removed (Fig. 1 and 2).

Breast cancer is often multifocal and may involve separate areas of the same breast. Inadequate mastectomy may leave foci of residual carcinoma. Equally disturbing is the situation in which a patient has had a so called "simple mastectomy" for a benign condition years earlier and later develops cancer in remaining breast tissue.

The anatomic extent of breast tissue varies with the age of the patient and the size of the breast. At its borders, breast tissue becomes a thin layer which may extend to the clavicle, the midline of the sternum, the border of the latissimus dorsi muscle and the costal margin. There is also an axillary tail of Spence (Fig. 3), which extends upward into the axilla through Langer's foramen. At times, breast tissue is located in the fascia of the pectoralis major muscle.

A proper simple mastectomy can be performed through an elliptical or transverse incision. The skin flaps should be thin so that all the superficial fascia is included in the operative specimen. The surgeon must excise breast tissue which reaches the midline of the sternum, the inferior border of the clavicle, the costal margin and the medial border of the latissimus dorsi. The axillary prolongation should also be included in the resection.

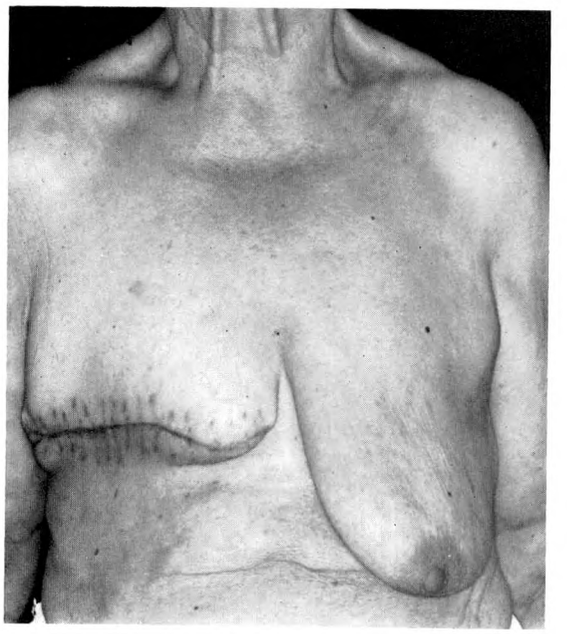


Fig. 2. Considerable breast tissue remains after "simple mastectomy."

The most recent report of incomplete simple mastectomy was made in 1940 by Hicken,[1] in which he proved that the breast tissue had not been removed in 17 patients

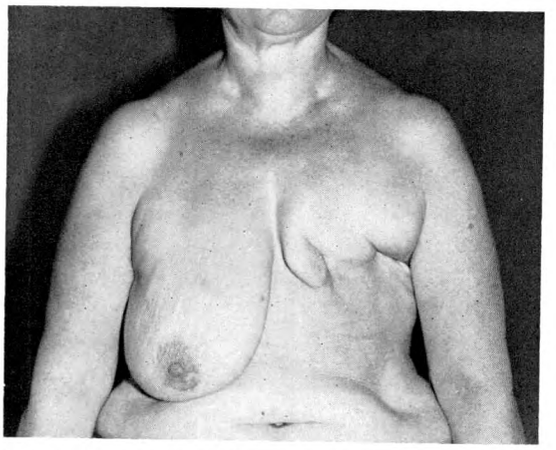


Fig. 1. Inadequate "simple mastectomy." Only protuberant breast has been excised.

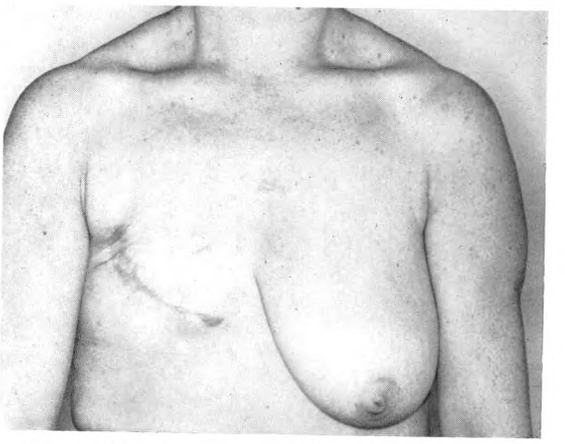


Fig. 3. The axillary tail of Spence has not been removed at time of "simple mastectomy."

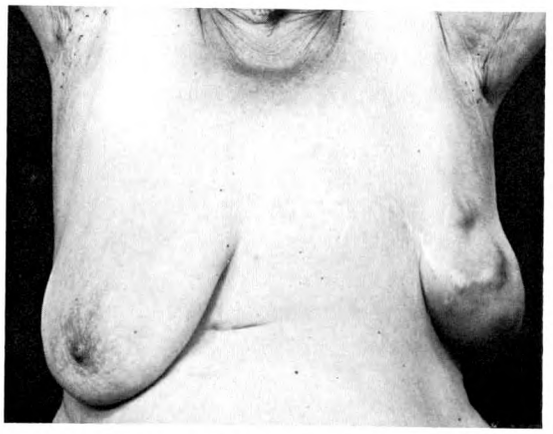


FIG. 4. Case 1. Cancer arising in lateral breast tissue after "simple mastectomy."



FIG. 5. Case 2. Cancer originating in residual breast tissue after right "simple mastectomy" for benign disease. Note also residual breast tissue on left side after "simple mastectomy."

who had simple mastectomy, by injecting dye and demonstrating that the duct systems had been severed. He also reported a case of cancer appearing in the axillary tail after a simple mastectomy had been done 15 years earlier.

Recently, we have seen 2 examples of similar situations which are representative.[2] The first, Case 1, was a 73 year old woman who had had a simple mastectomy done elsewhere in 1951 for a bleeding nipple. Ten years later she was seen at Memorial Hospital with a large mass in the lateral portion of the simple mastectomy scar (Fig. 4). A radical mastectomy was performed and the specimen showed cancer arising in residual breast tissue. The second, Case 2, was a 62 year old woman who had had a right simple mastectomy in 1951 for an intraductal papilloma and a left simple mastectomy for cancer in 1955. She was seen in Memorial Hospital in 1963 and examination revealed residual breast tissue bilaterally. In addition, there was a mass in the scar of the right simple mastectomy which had been performed for a benign condition. Right radical mastectomy was done and the specimen showed papillary carcinoma arising in residual breast tissue (Fig. 5).

CONCLUSION

The cited cases prove that breast cancer may develop in remaining breast tissue when an incomplete simple mastectomy has been done. We would like to urge that the term simple mastectomy be deleted from the medical nomenclature and be replaced by "total mastectomy" to emphasize that all breast tissue should be removed whether the operation is being performed for a benign or malignant disease.

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THE PARADOX OF BREAST CANCER*

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A PARADOX is a seeming contradiction which may be true in fact. This precisely describes the assertions that, while survival rates improve,[1,3,12,13,22] mortality rates for breast cancer are unchanged.[2] It is quite possible to accept both these well supported observations and to show the effectiveness of treatment free from contradictory evidence.

It is difficult to believe that a simple explanation could be overlooked but the answer appears to be in the illusory nature of the index called "survival rate" which has been relied upon as a measuring stick for determining the effectiveness of treatment.

The ultimate goal of cancer therapy is cure, but cure rate will not serve as an index of success for lack of confidence in the clinical assessment of cure. The cursory examination failing to disclose persistent cancer would favor apparent cure, while meticulous investigation leading to early discovery of a silent site of cancer would lower cure rate and falsely suggest that the treatment being evaluated was less effective.

Survival is seen as an absolute end-point that should render all reported series comparable and has become the single standard for evaluating effectiveness of treatment. Certain defects exist in survival rate as a substitute index for cure rate to be used in measuring the effect of treatment. While these defects are not really obscure, the summation of their effects are not commonly presented with the evaluation of clinical experience.

Any examination of the subject of the effectiveness of treatment is apt to arouse "fierce surgical passions"[15] and to avoid this obstacle to clarification, the explanation to be developed in this thesis may be divulged in the beginning. Treatment is not the sole element controlling the duration of survival. Whether other factors reinforce or nullify the effect of treatment, they do obscure it. More than the brand of fuel is involved in an economy run; more than treatment is involved in survival. Miles or years as criteria of success, without other facts, cannot prove the merit of any one component factor in the outcome. That some cancers are cured, that more could be cured and that treatment may increase survival, symptom-free, even if cure is not achieved, is not in doubt. Neither is this an issue in this presentation. This is an inquiry into why a paradox should exist in regard to ever improving survival rates and unchanging mortality; why a standard treatment technique should appear increasingly effective, and why treatment of different types should appear so similar in their effects. Not the treatment but the accounting is under investigation.

FACTORS INFLUENCING SURVIVAL

The period of survival is strongly influenced by 5 factors which are independent of treatment and which tend to mask the effect of treatment.

1. The count-down on survival begins at the time of treatment which coincides closely with the time of diagnosis. The effect of years of effort and education has been to shift the time of diagnosis to the left on the time scale. But even without treatment, earlier diagnosis means that the count-down on survival begins earlier and the survival time, as we measure it, is increased. Earlier diagnosis and earlier treatment must, of course, be given credit for cure when they forestall distant metastases. There may also be reason to think that the earlier the treatment is offered, the greater

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will be its effect upon survival even if cure is not achieved. But our inquiry here concerns the usefulness of survival rate as a measure of treatment effect.

Earlier diagnosis permits earlier treatment and, quite apart from any effect of treatment, the survival time is increased. The patient may not live longer but she lives longer as a cancer patient. Equal advantage of the improvement in earlier diagnosis that has occurred over the years exists only for patients presenting for diagnosis in the same time period. The effect of earlier diagnosis on prolonging the survival period as distinguished from the effect of earlier treatment to actually prolong life can only be discounted for synchronous series of patients.

2. The crucial factor in achieving cure by a particular treatment is whether or not metastases have occurred in a site beyond the possibility of eradication by the treatment. If such an extension of the disease is known to exist, the case is deemed untreatable or, at least, treatment is not offered with curative intent. Occult metastases are the principal cause of failure of every form of treatment now in use. Patients who are clinically eligible for curative treatment really consist of 2 indistinguishable classes: (a) those who have occult distant metastases and for whom no treatment, constrained by anatomic limitations, could achieve complete eradication and cure; and (b) those whose disease is confined to the area which will be affected by the treatment offered and for whom treatment may fail or succeed according to the skill or policy involved.

Could the second group be analyzed separately, the incidence of success or failure would be an index of effectiveness of treatment. If the classes are of equal size and if, for class (b) treatment "X" succeeds in 10 per cent more patients than treatment "Y," then success would appear as only 5 per cent improvement when treatment must be offered to classes (a) and (b) combined because they cannot be distinguished. If, of the total number, only 1/5 are in class (b), then an improvement of 10 per cent for class (b) would appear as only 2 per cent improvement in the total and would be very difficult to recognize.

The presence of occult distant metastases in some proportion of any group of clinically operable patients precludes success for these unidentifiable patients by any type of treatment that may be offered. If a difference does exist as to effectiveness in eradicating the disease in those patients with cancer still localized to an accessible volume, the real difference in survival in this fraction of the group is masked when survival rate must use the total number as a denominator. The presence or absence of occult metastases at the time of treatment may have a more powerful effect on survival rate than does treatment itself.

3. Survival is intimately related to degree of malignancy or rate of growth, and the range of malignancy for breast cancer is very great. The advantage of a meticulous treatment technique performed on breast cancer still localized to accessible tissues may be of crucial importance while the primary cancer and its metastases are still localized but the subsequent course of the disease will still be brief for a rapidly growing cancer with distant occult spread. Conversely, a slowly growing breast cancer, uncured through failure of unskilled or inappropriate treatment will, by the patient's long survival, be counted to the credit of the faulty method. There is an illusion in contrasting short and long survival, culminating in recurrence; both are equally failures.

The grade or degree of malignancy dictates the duration of survival in uncured patients. When survival rate is the criterion of effectiveness of treatment, variations in the range and distribution of malignancy mask the differing effectiveness of treatment as between otherwise comparable series.

4. Error in diagnosis may be in either direction; a benign lesion may be called malignant or a malignant lesion called benign. The first type of diagnostic error is

unlikely to be detected when treated by curative surgery because "nothing succeeds like success;" there is no reason to question the result in the happy patient who returns free of disease for many years. The second type of error shows itself by the inevitable progress of the untreated cancer. Diagnosis and treatment for such patients have been deferred, or shifted to the right on the time scale, and so, the measured span of survival is shortened.

Concern for the influence of errors in diagnosis is not new. Writing in 1837, McFarlane[18] said, "In some of these cases even the most experienced may be deceived, and be led, from the disease not having returned, to assign more value and importance to the operation, than it is justly entitled to, and thus to take credit for cures which were never performed."

That error in interpretation of histologic preparations does occur is accepted even though it may arouse some "fierce pathological passions." When Garland raised the question whether 5 year survival rates of 44 per cent in California might be artificially high because of the inclusion of a significant number of benign lesions, a survey of the histologic basis for diagnosis of breast cancer in the California Tumor Registry was undertaken. Linden *et al.*[17] reported the findings: "If the entire group of 1,451 cases were studied, the proportion of cases of breast cancer confirmed by the reviewing pathologists would be between 85.4% and 95.4% ($90.4 \pm 2[2.5\%]$). The percentage 90.4% can be used as the best estimate for the entire group of patients with confirmed breast cancer during the period 1942–1948, with at least 5 years survival."

This is not entirely reassuring because it appears to mean that 10 out of 100 lesions diagnosed as breast cancer are likely to be benign. Since nearly all these patients may be expected to survive for 5 years, a reported 5 year survival rate of 44 per cent may mean that the survival rate for patients who actually have breast cancer is around 38 per cent.

The validity of the query is illustrated by range of opinion encountered when dealing with the question of benign lesions versus cancer for specific lesions. The burden of decision is a heavy one and the pathologist may weigh the histologic evidence in the light of possible consequences. "It is recognized that the borderline of diagnosis between benignancy and malignancy in papillary growths is an undulating one and some pathologists, to be safe, call them all cancer."[21] "A generous policy of operating on doubtful or clinically benign lesions of the breast will improve the cure rate of breast cancer, mainly by affording better material in which the cancer is more likely to be confined to the breast and its regional lymph node deposits in the absence of established systemic spread."[23] Whether by mistake or policy, any appreciable series of patients treated for breast cancer will contain some instances of benign lesions treated as malignant lesions. The effect is to impose a penalty upon the series with the greatest number of correct diagnoses because only a true cancer called benign is a self-correcting error.

Errors in diagnosis do exist and tend to mask the real value of effective treatment. If there is any bias, the error is apt to be in the direction of a benign lesion being identified as cancer, the mistake that is not self correcting. The more errors of this type in a series, the better will be the survival rate. The best pathologist is a handicap in a comparison of survival rates.

5. Survival rates are of course based upon all the patients treated, including those who, in time, are shown to be uncured. For these patients, roentgen-ray therapy, chemotherapy, hormone therapy and endocrine surgery are offered. From the evident effect on life-threatening aspects of the advancing disease, an effect to prolong life must be recognized for at least some patients.

Survival is prolonged by modern supportive therapy, but survival rates based on patients receiving such benefits will mask the relative effectiveness of the pri-

mary treatment for purposes of comparison.

PROPOSED INDEX FOR DETERMINING EFFECT OF PRIMARY TREATMENT OF BREAST CANCER

It is apparent that reliance upon survival rate has obscured the effectiveness of treatment but reappraisal of results and reporting may establish the relative merit of current techniques. An index to measure the effect of treatment alone should be free of the influence of the 5 factors that have been discussed. The information is available in the files of any hospital where patients have been followed carefully after it became evident that their cancer of breast was uncured.

Since all primary therapy is directed toward eradication of disease locally, the criterion of effective treatment is freedom from evident disease in the treatment site at the time of death.

1. The duration of survival does not enter into determination of whether evident cancer persists in the treatment site at the time of death. There is no occasion to distinguish the effect of early diagnosis from the effect of early treatment on prolongation of life.

2. The criterion of effective treatment is the absence of disease in the treatment site; the presence of distant metastases does not detract from the value of treatment that achieved success in the area where it was applied.

3. The duration of the course of the disease is not a factor; malignancy or rate of growth does not influence the appraisal of effectiveness of treatment.

4. The patient who dies of the disease proves the diagnosis. The patient who dies of the disease without cancer in the treatment site proves the effectiveness of the treatment at that site.

5. Treatment of the uncured patient may affect the survival period, but it does not invalidate the appraisal of local recurrence as an index of effective primary treatment. Even if treatment of a local recurrence should be successfully undertaken, so that none was present in the primary site at the time of death, the record will show that the primary treatment alone did not achieve local eradication.

Table 1 shows the number of local recurrences among 425 patients who died of breast cancer. All were patients referred to the radiotherapy department for prophylactic radiotherapy or for treatment of known disease. All patients had been clinically operable when first seen and had been treated by radical mastectomy with curative intent. At some time in the course of their disease, it became evident that they were uncured and they were followed to time of death. In this group, 255 (60 per cent, $\sigma = 10$ cases or 2.5 per cent) showed no evidence of local recurrence at any time during the entire follow-up period.[7,8]

The influence of these 5 factors upon survival rate is predictable. In general, there are two types of study.

(1) In asynchronous studies, series of patients in successive or different time periods are studied for comparison of similar or different methods of treatment offered at different times. The effect of the 5 factors is to mask the actual effect of treatment. Later series may be expected to

TABLE I

LOCAL RECURRENCE IN 425 PATIENTS TREATED BY RADICAL MASTECTOMY AND FOLLOWED TO DEATH

Radiotherapy	Total No. of Patients	Local Recurrence	No Local Recurrence
Preoperative	50	15 (30%)	35
Postoperative	178	63 (35%)	115
Both pre and postoperative	15	5 (33%)	10
For metastases only	182	87 (47%)	95
	425	170 (40%)	255 (60%)

show improvement in survival rate since diagnosis is likely to be at an earlier stage in the course of the disease. Greatest improvement is in comparison with earliest series and lesser improvement attends comparison of later series.

(2) In synchronous studies, the patients may have been treated in different institutions or by different methods, but they have presented themselves within the same time period. Such patients will have equal advantage of the level of cancer education of their day, and of the advances in cancer diagnosis and treatment of uncured patients. The unchanging elements of breast cancer, the effect of occult distant metastases and of variation in degree of malignancy will be the masking elements in a comparison of different treatment methods.

When a comparison is made between two time periods during which some progress has been made in educating the public to seek medical attention earlier, the cases in the later group will be those for whom the count-down on survival begins earlier; the survival period so determined will appear longer; the survival rate will appear improved. If the comparison is between successive periods in the same institution and by the same treatment method, then the report will show encouraging "improvement" in "results." This will be attributed to the advantage of treating earlier when it is, in fact, due to diagnosing earlier. If no change in treatment policy has occurred, the improved survival rate will be attributed to the advantage of earlier diagnosis. If there has been a change in personnel or treatment policy, then new skills and new techniques will receive credit.

If the comparison is between the 5 year survival rates in different institutions, then the institution reporting on the later series of patients will have the advantage. If there is no actual improvement in the effectiveness of the innovation, it will appear better by virtue of the earlier diagnosis. If it is indeed less effective, it may appear at least as good with the help of an assist from earlier diagnosis.

There are limits to what can be achieved by public education in the matter of earlier diagnosis. The curve of improvement will be steep at first and then tend to level off. In comparisons of survival rates during the transition period between social suppression of cancer information and public response to the educational campaign, the opportunity for much earlier diagnosis for many individuals will be related to dramatic improvement. Once public education has reached a high level, the gleaning of still earlier diagnosis will be thin. In the first period all results improve; in the second all results approach stability.

In a carefully planned comparison of different treatment techniques, using alternate cases or random selection in the same institution, the result is predictable. The method enforces a uniform effect on the 5 factors—time of diagnosis, occult distant metastases, degree of malignancy, errors in diagnosis and treatment of uncured patients. The only factor allowed to vary is treatment. But the effect of treatment is a pea under a thick mattress of other factors and our 5 year survival rate, being a peasant rather than a princess, is insensitive to the masked and buried actual effect of treatment. Thus, an astonishing similarity appears between the effects of vastly different treatment policies, and the sophistication of the treatment design overwhelms the thread of reason that clinical experience and judgment might attempt to exercise.

The first reports to be discussed are examples of asynchronous studies from the same institution or locale. In some, the treatment policy is unchanged; in others it has been modified. The series which occurs later in time always shows improved or equal survival rates whether treatment policy is unchanged, more radical or more conservative.

Earlier series generally reported consistent and encouraging results of radical mastectomy. In Harrington's[18] series, the 5 year survival rate of 39.7 per cent for patients treated 1910–1914 was improved to 52.4 per cent for patients treated 1940–1944. Adair[1] reported 34.0 per cent 5 year

survival rate for patients treated in 1935 with improvement to 42.0 per cent for those treated in 1942. Recently, Randall, speaking from the same experience, has been quoted as stating that "no matter how advanced the cancer, provided it can be operated at all, there is a 65% five year survival rate. This is almost twice as good as the survival rate 50 years ago."

Haagensen *et al.*[12] reported on two periods, 1935–1951 and 1952–1955, with 5 year survival rates of 68.5 per cent and 82.2 per cent, respectively. It is explained that this is due to increasingly strict methods of selection in an effort to achieve a higher cure rate, but there is an implication of improvement in the highest reported 5 year survival rate for a series of breast cancer.

Anglem and Gray[3] reported two series of patients treated by radical mastectomy, 1939–1948 and 1949–1953, with survival rate improving from 62.4 per cent to 74.5 per cent. These authors state that "patients are coming to the surgeon in substantially earlier stages of disease. This is reflected by a significant improvement in survival rates over those reported from earlier periods. Since there has been no significant change in treatment methods, this improvement is almost wholly due to education of the public to seek early treatment." This is very clear support for the proposal that earlier diagnosis masks the effect of treatment. If, as the authors state, the improvement is almost wholly due to education of the public to seek early treatment, then, (a) this improved survival rate is due to earlier diagnosis and not to treatment, (b) any treatment offered under these circumstances would appear to be associated with improved results, and (c) if any difference in the treatment offered in the two time periods influenced survival of either group, the effect would be masked by the apparent improvement in the later group.

Lewison[16] reported a modest improvement in 5 year survival rate from 44 per cent to 52 per cent for the period 1935 to 1950 at Johns Hopkins Hospital and, in a careful and critical review of the literature, noted a striking similarity and surprising uniformity of end results in the treatment of breast cancer despite widely differing therapeutic techniques.

Auchincloss[4] reviewed the results of very wide skin and subcutaneous tissue removed, and the more radical operation with dermal dissection among patients treated at Presbyterian Hospital in New York and came to the conclusion that "operation of radical mastectomy is unnecessarily radical. The thorough axillary dissection which it affords accomplishes nothing for the survival of patients with breast cancer that a more limited operation would not do equally well."

The second group of reports deals with studies of synchronous series of patients. These may be retrospective studies of all patients treated during a given time period in an institution or locale by various individuals and techniques. It may be a controlled series where an effort is made to ensure the similarity of patients being treated by the techniques to be compared. These show a predictable similarity because the actual effect of treatment is masked by the overpowering influence of other factors in survival and survival rate.

The Rockford series by Smith and Meyer[20] is a synchronous statistical study of 432 cases of breast cancer in the community in the period 1924–1952. The predictable conclusion was, "Neither the five- nor ten-year survival rates were affected by the type of operation, the duration of the tumor or the skill of the surgeon." Their candid comment was, "The confusion in our minds relating to the treatment of cancer of the breast has not been resolved by this study."

Cole[6] reported on the 7 year survival rate of two groups of patients with breast cancer, randomly selected (and synchronous). Both had had a standard radical mastectomy and no clinical evidence of residue or metastases on examination after operation. One group received postoperative radiotherapy and the other did not. There was no difference in mortality rate

or the incidence of distant metastases.

The report on breast cancer from the Yale-New Haven Medical Center by Goldenberg *et al.*[10] from 1921–1957 is a synchronous comparison of simple mastectomy and radical mastectomy. The survival rates at 5 years were equally good and the age corrected difference at 10 years could be accounted for solely on the basis of random variation.

Crile[9] in 1955 adopted simple mastectomy without irradiation therapy as a standard treatment for patients with no clinical evidence of cancer beyond the breast, and compared his results with the synchronous experience of his colleagues at Cleveland Clinic, using radical mastectomy in similar cases. He concluded that, for Stage I cancer of the breast, simple mastectomy without prophylactic irradiation appeared to be at least as effective as radical mastectomy with or without irradiation. He comments, "It is not clear why simple operation without irradiation appears to control breast cancer as well as radical ones with irradiation."

In the Copenhagen study reported by Kaae and Johansen,[14] alternate patients with breast cancer were treated after the McWhirter technique of simple mastectomy and radiotherapy or with the extended radical mastectomy including dissection of the supraclavicular region and internal mammary chain. In equal groups of 182 patients, the 5 year survival rates were 54 per cent and 55 per cent, respectively, for treatment techniques so radically different that one might expect operative mortality alone to produce some difference in survival rate. This report offers additional information on recurrence-free survival—44 per cent and 38 per cent, respectively. This is revealing even without information on the incidence of local recurrence at the time of death for nonsurvivors. This provides some basis for choosing between conservative and radical treatment, a choice which could not be made on a consideration of 5 year survival figures alone.

Paterson and Russell[19] designed a clinical trial to determine the actual value of prophylactic radiotherapy following radical mastectomy, based on a random selection among 1,461 patients. They reported no statistically significant over-all differences in crude mortality rate at 5 years between those patients treated by radical mastectomy plus prophylactic radiotherapy and cases "watched" and treated only on need. They noted that the incidence of local recurrences was reduced in patients receiving prophylactic irradiation but of course no similar incidence for patients dying of the disease is mentioned.

Lastly, the series of breast cancer patients treated by Guttmann[11] with irradiation alone rounds out the variety of possible treatment that could be offered to a primary breast cancer and the adjacent lymphatic drainage areas. These were patients considered inoperable by the strict criteria of Haagensen *et al.*[12] and referred to radiotherapy after biopsy alone. The 5 year survival rate for 48 patients was given as 54.2 per cent. This makes interesting comparison with the series of other individuals and institutions,—extended radical mastectomy in Copenhagen, 55 per cent, simple mastectomy and irradiation in Copenhagen, 54 per cent, and Haagensen's comparable personal series of "operable" cases with positive axillary lymph nodes, 52 per cent. As Lewison[16] noted, the similarity of these statistics is "incredible," but is also explicable as a comparison of synchronous series in different institutions.

SUMMARY

An explanation is proposed for certain paradoxical observations on the course of treated breast cancer whereby, in the face of unchanging mortality rates, it appears that treatment is continually improving, yet all treatment methods have identical effect, or none at all.

This paper does not propose that treatment of breast cancer is ineffective.

This paper does propose that the effect of treatment cannot be determined by survival rate.

The paradox results from reliance on survival rates.

The first effect of earlier diagnosis and treatment is to lengthen the survival period by beginning it earlier; survival rate improvement is then credited to whatever treatment is offered. Occult metastases, rate of growth, errors in diagnosis, and treatment of uncured cancer all exert an influence on survival which masks the effect of treatment.

When treatment methods in asynchronous or successive periods are compared, the most recent series will always show a better survival rate as long as education and cancer detection continue to produce ever-earlier diagnosis.

When treatment methods in synchronous or simultaneous periods are compared, the masking factors obscure the actual effect of all treatment equally.

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VOL. 99, No. 4

THERAPEUTIC INTEGRATION OF BREAST CANCER*

ANALYSIS OF 174 CASES

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THE problem of breast cancer at the Hospital Español, México, D.F. is managed with 3 approaches: (1) detection; (2) individualization of treatment, using cancerologic criteria for evaluation of operability; and (3) surgery and radiation therapy carried out by the same team.

CANCER DETECTION

In July 1952, a Breast Cancer Detection Clinic was started at the Hospital Español, which was separate from the Department of Neoplastic Diseases. The work done until December 1963 is presented in this paper. A series of 1,098 persons (men and women) was studied, of which 615 were symptomless and 462 had some symptoms. Twenty-one patients whose breast cancers were previously treated in other institutions are included (Table I).

Table II shows that out of the 615 patients without symptoms, 6 (0.99 per cent) had breast cancer which was histologically verified. Perhaps their symptoms were concealed; however they did not go to a Tumor Clinic, but reported to a Detection Center instead.

TABLE I

RESULTS OF DETECTION OF BREAST CANCER AT THE HOSPITAL ESPAÑOL DETECTION CENTER OF MAMMARY NEOPLASIAS

(July 2, 1952–December 31, 1963)

Total number of persons examined for the first time		1,098
Number of persons totally symptomless	615	
Number of persons with some symptomatology	462	
Number of patients with breast cancer, but whose initial therapy was done in other Institutions	21	
	1,098	

TABLE II

DIAGNOSIS DISTRIBUTION IN 615 SYMPTOMLESS WOMEN

I. Patients without apparent neoplasias			531	
II. Patients with benign mammary neoplasias	Fibroadenosis with histologic diagnosis	23	68	Patients with definitive diagnosis: 605
	Cystic disease of the breast	15		
	Fibroadenosis without histologic diagnosis	13		
	Fibrolipoma	6		
	Fibroadenoma	4		
	Ectopic axillary mammary gland	4		
	Inflammatory lesions	3		
III. Patients with malignant mammary tumors			6	Percent of malignancy: 6/605=0.99%
IV. Patients with mammary tumor but who refused therapy			10	
		Total	615	

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
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TABLE III

DIAGNOSIS DISTRIBUTION IN 462 SYMPTOMATIC PATIENTS

I. Patients without apparent neoplasias			108	
II. Patients with benign mammary neoplasias	Cystic disease of the breast	68	248	Patients with definitive diagnosis: 433
	Fibroadenoma	65		
	Fibroadenosis with histologic diagnosis	51		
	Prepuberal mastitis	12		
	Gynecomastia	8		
	Fibrolipoma	7		
	Ectopic axillary mammary gland	7		
	Fibroadenosis without histologic diagnosis	6		
	Intraductal papilloma	5		
	Plasma cell mastitis	2		
	Breast tuberculosis	1		
	Inflammatory lesions	16		
III. Patients with malignant mammary tumors	Cancer	76		Percent of malignancy: 77/433 = 17.7%
	Cystosarcoma phylloides	1	77	
IV. Patients with mammary tumor but who refused therapy			29	
		Total	462	

The diagnoses of the 462 patients who were symptomatic are shown in Table III. Of this group, 77 (17.7 per cent) were found to have breast cancer.

CLINICAL MATERIAL

The total number of patients with breast cancer was 341; however, only 184 were treated by us from the beginning and of

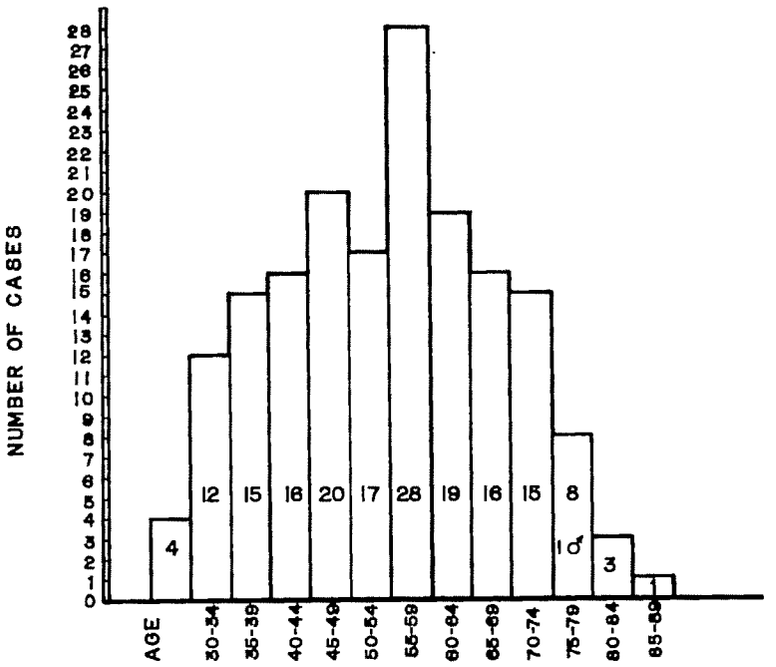


FIG. 1. Age histogram of 174 cases of breast cancer.

TABLE IV

SOME OF THE GYNECOLOGIC-OBSTETRIC AND LACTATION CHARACTERISTICS IN 173 WOMEN WITH BREAST CANCER

	Total Number of Patients			
No Lactations	77	Single Married Childless Married with Children		38 29 10
		Complete >6 Months	One Lactation Multiple Lactations	10 44
		Incomplete <6 Months	One Lactation Multiple Lactations	4 13
		Both		10
Not Investigated	15			

these 10 had files without sufficient information, leaving 174 patients for analysis. Figure 1 is an age histogram of these 174 patients, showing that the highest incidence occurred in the 55 to 59 year age group.

Table IV contains data on some gynecologic-obstetric and lactation characteristics. The distribution according to the single or married status is not easy to establish, since, in the population to which these women belong, the value of this ratio is not known. Thus, there is a large number of single women in this cancer group, and the ratio of 38/173, or 21.8 per cent, is perhaps too high. The same applies to the significance of lactations.

Table V gives the hormonal data. The group of patients who received estrogens is greater than that which received androgens. Possibly the former are associated with tumor development, or perhaps the tumor and the need to prescribe estrogens are linked to an equal cause.

Table VI shows the familial tumor relationship. It seems very important to us that 44.7 per cent of our patients had had previous cases of tumors in their families (in the first and second generation of progenitors). This is a higher incidence than one would expect.

BREAST CANCER AND MENOPAUSE RELATIONSHIP

Table VII indicates that 59 of our patients were premenopausal and 114 were

TABLE V

PREVIOUS HORMONE ADMINISTRATION IN 174 CASES OF BREAST CANCER

Without Hormone Administration	104			
With Previous Hormone Administration	37	♀	24	24/174=13.7%
		♂	8	8/174=4.59%
		♀ ♂	5	
Not Investigated	32			

TABLE VI

FAMILIAL INCIDENCE OF TUMORS (IN THE FIRST OR SECOND GENERATION PROGENITORS) IN 174 CASES OF BREAST CANCER

Mammary Cancer	20	20/174= 11.4%	78/174=
Non-Mammary Cancer	58	58/174= 33.3%	44.7%
Without Previous Familial Malignant Neoplasias	80	80/174= 45.9%	
Not Investigated	23		

postmenopausal. We think it of interest to relate the time elapsed between the menopause and the age of onset of cancer.

Figure 2 shows the index we have established for this: *I* is the index of "ovarian estrogenic penetration," *b* is the age at which breast cancer was diagnosed, and *a* stands for the menopause.

We know that the menopause does not signify the absence of estrogenism, but it is no less true that this index represents an estimate of the ovarian estrogenism in the patient's life. In other words, we measured the interval "menopause-cancer" in the menopause unit.

Figure 3 shows the histogram of the evaluation of *I*. The greatest number of patients is between the index values of 0 and 0.4; *i.e.*, between the limits that represent the highest values of the index, even though the mathematical device makes it correspond to the minor digits.

TABLE VII

DISTRIBUTION OF 173 CASES OF BREAST CANCER ACCORDING TO TIME ELAPSED BETWEEN MENOPAUSE AND AGE OF ONSET OF CANCER

Premenopausal Patients		59
Postmenopausal Patients	From 0 to 1 year after menopause	3
	From 1 to 5 years after menopause	24
	From 5 to 10 years after menopause	16
	From 10 to 15 years after menopause	16
	From 15 to 20 years after menopause	12
	From 20 to 25 years after menopause	5
	From 25 to 30 years after menopause	2
	For more than 30 years after menopause	10
	Years of menopause ignored	26
	Total	173

CLASSIFICATION OF THE CLINICAL MATERIAL

Table VIII is Haagensen's anatomoclinical classification of breast cancer, which we use; and Table IX shows the distribution of our material based on this classification. It can be seen that it does not favor any Stage; however, Stages A and B added, represent 54.0 per cent of the total.

THERAPEUTIC CRITERIA

The rules employed in establishing therapeutic criteria are: (1) individualization of the case; and (2) limitation of primary surgery to those patients who do not constitute surgical contraindication in the cancerologic meaning, even if they are technically operable.

Table X lists the clinical criteria of operability according to Haagensen and Stout.[5] It may be noted that some of the criteria singly exclude surgery, others do so only if an associated sign is present. If

$$I = \frac{b-a}{a}$$

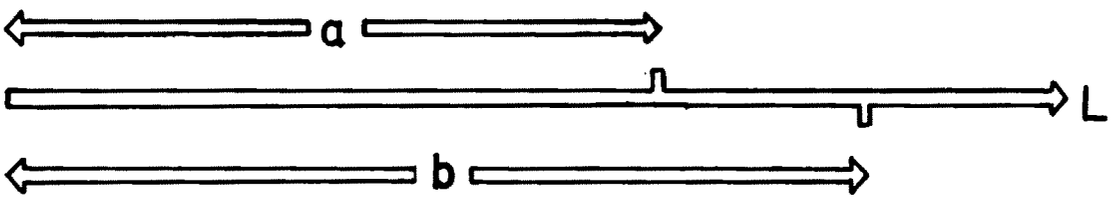


FIG. 2. "Ovarian estrogenic penetration" in the life of the patient (see text). I = index of "ovarian estrogenic penetration" in the life of the patient; b = age of onset of cancer; a = menopause; L = survival of the patient.

surgery is not used, we proceed with radiation therapy. Then, if the barring criteria disappear we operate; otherwise, we continue with irradiation and eventually add hormonal therapy.

The initial decision as to the method of treatment to be employed is made by the same team, even though some of its members are surgeons preferring operation, while others tend towards use of radiation therapy. As a team, however, they observe the clinical criteria described above on the theory that the therapeutic approach decided upon must be the result of a planned integrated strategy, and not of individual preferences and capabilities.

METHOD OF TREATMENT

Surgery is performed according to the Halsted-Haagensen principles. The operative mortality has been 1 case in 137 radical mastectomies, or 0.7 per cent (a case of surgical shock in 1947).

Ultraradical surgery with dissection of the internal mammary blocks is not done because it contributes very little to the curability of breast cancer. Likewise, we do not use simple mastectomy, and the cases where it was practiced will be discussed.

Biopsy is taken at the time of the operation, from the mammary tumor, and from the supraclavicular fossa when there is

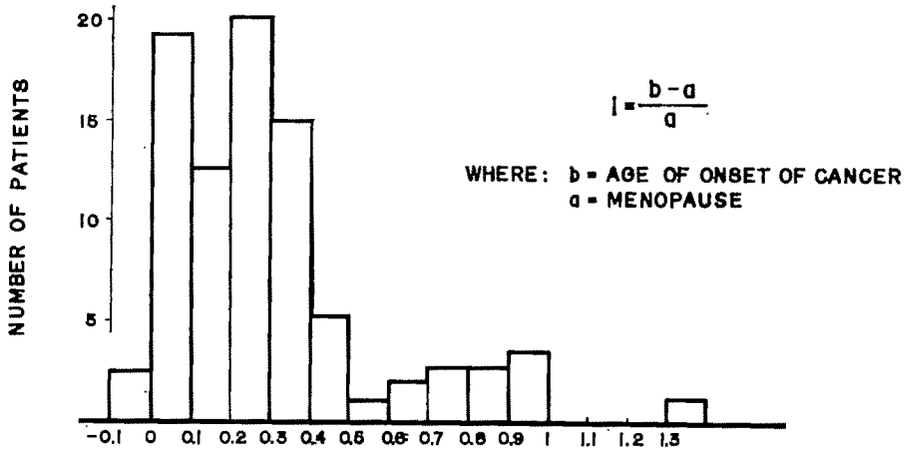


FIG. 3. Frequency histogram of distribution in 173 cases of breast cancer based on the index value of "ovarian estrogenic penetration" (see text).

TABLE VIII

CLINICAL CLASSIFICATION USED[4]

Stage A. There is not:

1. Skin edema
2. Ulceration
3. Solid fixation of tumor to chest wall
4. Clinically involved axillary lymph nodes

Stage B.

1. The same as Stage A except for
2. Clinically involved axillary lymph nodes, less than 2.5 cm. in transverse diameter and not fixed to overlying skin or deeper structures of the axilla

Stage C. Any one of these signs:

1. Skin edema (less than ⅓ of the skin over the breast)
2. Ulceration
3. Solid fixation of tumor to chest wall
4. Massive involvement of axillary lymph nodes (2.5 cm. or more in transverse diameter)
5. Fixation of the axillary lymph nodes to overlying skin or deeper structures of axilla

Stage D.

1. A combination of any two or more of the five grave signs listed in Stage C
2. Extensive edema of the skin (involving more than ⅓ of the skin over the breast)
3. Satellite skin nodules
4. The inflammatory type of carcinoma
5. Supraclavicular metastases (clinically apparent)
6. Parasternal metastases (clinically apparent)

suspicion of metastatic lymphadenopathy. The findings of these 2 biopsies, together with the clinical criteria, form the basis of our evaluation of operability.

TABLE IX

DISTRIBUTION OF THE PATIENTS ACCORDING TO THE CLINICAL STAGING

Stage	Total No. of Patients
A	41
B	53
C	35
D	45
	174

Radical radiation therapy is carried out in continuity by including those zones eventually involved and avoiding exposure of discontinuous zones.

Table XI gives a detailed compilation of the therapeutic modalities used in the 174 cases of breast cancer.

Group 1 contains 8 patients with early carcinomas of the outer quadrants of the breast, and where the operative axillary blocks showed no evidence of involved lymph nodes.

Groups 2 and 3 comprise a total of 102 patients in whom postoperative irradiation was undertaken because of the presence of axillary lymph node involvement or because the primary tumor was situated in the inner quadrants of the breast, or both.

The 8 patients in Groups 4 and 5 are: 5 cases with a high surgical risk and early carcinomas; 2 cases in Stage D, where we did simple mastectomy in order to eliminate, for palliative reasons, an ulcerated breast which caused great suffering to the patient; and 1 case in Stage A, where the

TABLE X

CLINICAL CRITERIA OF OPERABILITY[5]

Any woman, at any age, with cancer of the breast and who does not offer a very high surgical risk, should be treated by radical mastectomy, except when:

1. Extensive edema of the skin over the breast is present
2. Satellite nodules are present in the skin over the breast
3. The carcinoma is of the inflammatory type
4. Parasternal tumor nodules are present
5. Proved supraclavicular metastases are present
6. There is edema of the arm
7. Distant metastases are demonstrated
8. Any two, or more, of the following grave signs of locally advanced carcinoma are present:
   a) Ulceration of the skin
   b) Edema of the skin of limited extent (less than one third of the skin over the breast involved)
   c) Solid fixation of the tumor to the chest wall
   d) Axillary lymph nodes measuring 2.5 cm., or more, in transverse diameter
   e) Fixation of the axillary lymph nodes to the skin or the deep structures of the axilla

pathologist, after informing us at the time of operation that the tumor was benign, 4 days later reported a minimal carcinomatous area. We do not feel that it is important to separate these patients from the rest, since they are few in number.

Groups 6, 7, 8 and 9, corresponding to preoperative irradiation, will be analyzed later when evaluating the results obtained.

Groups 10 and 11 include the patients with very far advanced carcinoma associated almost always with systemic dissemination and in whom irradiation and hormonal therapy were the only advisable methods of treatment.

We do not have any experience with suppressive surgery of the adrenal and pituitary glands.

ANALYSIS OF THE RESULTS OBTAINED

Figure 4*a* is a diagram of the individual survival of patients in Stage A, grouped yearly. It also indicates whether the pa-

TABLE XI

THERAPEUTIC MODALITIES USED IN 174 CASES OF BREAST CANCER

1. Radical surgery alone	8
2. Radical surgery and postoperative roentgen therapy	70
3. Radical surgery and Co^{60} teletherapy (since 1959)	32
4. Simple mastectomy and postoperative roentgen therapy	3
5. Simple mastectomy and Co^{60} teletherapy	5
6. Preoperative roentgen therapy, radical surgery and postoperative roentgen therapy	10
7. Preoperative roentgen therapy, radical surgery and Co^{60} teletherapy	2
8. Co^{60} teletherapy, radical surgery and Co^{60} teletherapy	1
9. Preoperative roentgen therapy and simple mastectomy	6
10. Roentgen therapy and hormonal administration	34
11. Co^{60} teletherapy and hormonal administration	3
Total	174

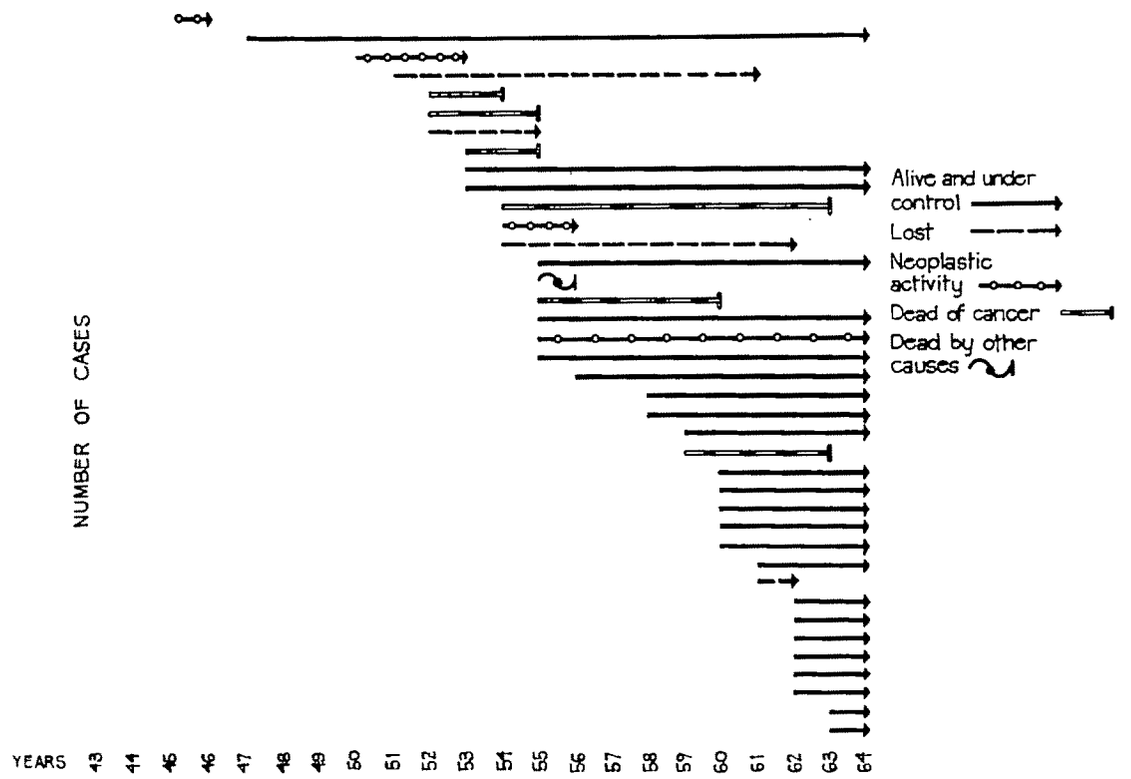


FIG. 4*a*. Survival diagram of patients in Stage A.

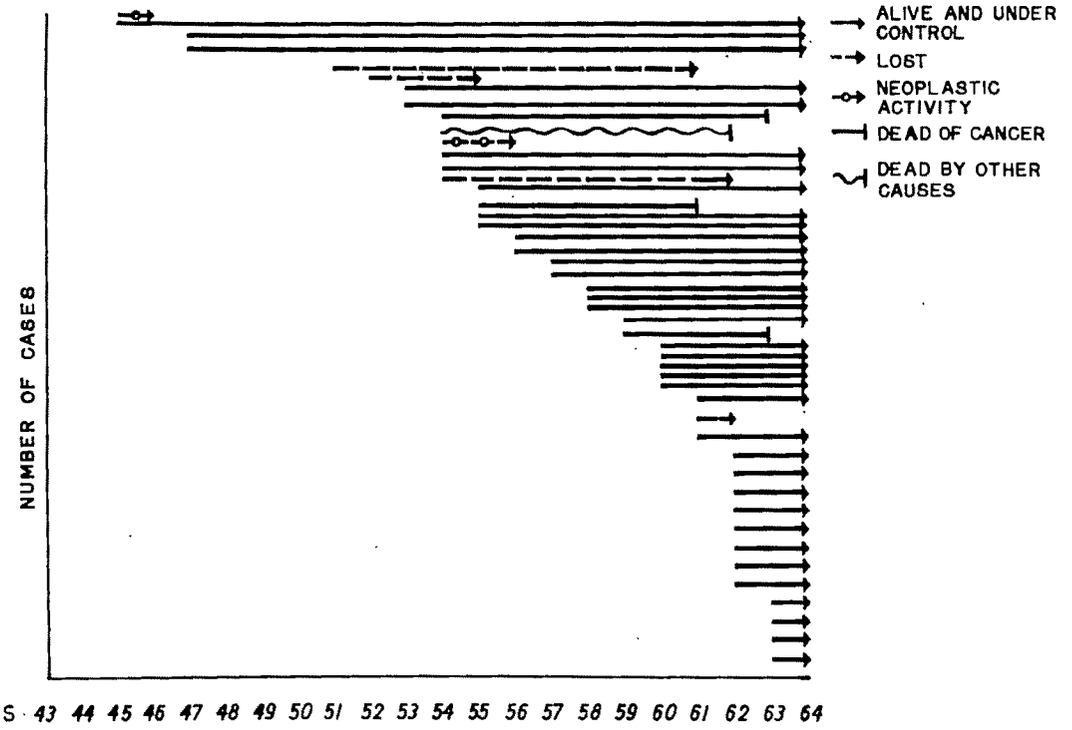


Fig. 4*b*. Survival diagram of patients in Stage A (48 patients) based on histopathologic study of the surgical specimen.

tient is under observation or lost to follow-up, and whether there are signs of neoplastic activity or not.

Figures 5*a*, 6 and 7 give the same information for Stages B, C and D.

Figure 8*a* shows the survival curves for the individual Stages, as well as the total survival curve of the studied material.

The results were evaluated by the actuarial method, which was described by Berkson and Gage (1950), Cutler and Ederer (1958), and García *et al.* (1962). This method consists of: (1) rising all the survival intervals of the patients, so that each one contributes in its known survival to the corresponding intervals; and (2) estimating the survival as a function of the concept "exposed to risk," calculated for each of the initial moments of the studied intervals. Such procedure allows a maximum gain of possible information from the data given by the material, lessening the mistakes due to small numbers.

Figure 8*a* shows that the curves for Stages A and B are almost the same, which would mean either that they correspond to the same group of patients, artificially separated by a useless criterion of classification, or that the existence of axillary lymphadenopathies would not modify curability.

As this latter possibility would seem unlikely, a new review of the patients was done, based on the histopathologic study of the surgical specimens as regards invasion of the axillary lymph nodes.

We then found that: (1) 7 of the 39 patients in Stage A had metastatic axillary lymph nodes, *i.e.* 7/39 were false negatives; and (2) in 17 of the 52 patients in Stage B the enlarged lymph nodes did not contain tumor, *i.e.* 17/52 were false positives.

Figures 4*b* and 5*b* show individually the new distribution in Stages A and B based on the histopathologic examination of the surgical specimens.

Figure 8*b* shows the new individual and over-all survival curves, according to his-

topathologic study of the axillary dissection blocks. It can be seen how the new curves for Stages A and B separate themselves considerably; this means, as could well be anticipated, that the existence of axillary lymph node metastases produces a clear lowering of curability.

The high level of survival curve for Stage A indicates the great value of early detection. On the other hand, the level of survival curve for Stage B, in its descending segment, is almost the same as that for Stage C; perhaps here the classification criterion is not sufficiently effective as to distinguish the differences of tumoral progression that are decisive for prognosis. Of course, we have not excluded personal mistakes in physical examination. This anatomopathologic analysis has been made to establish a more correct correlation between tumor progression and curability, not to rectify the clinical classification which is unchangeable.

TABLE XII

FIVE AND 10 YEAR CURE RATES, WITH THE CORRESPONDING STANDARD ERRORS (NUMBERS BETWEEN PARENTHESES)

Stage	Number of Patients	Cure Rate	
		Alive and Well 5 Years	Alive and Well 10 Years
A	48	94.1 (±4.2)	75.4 (±10.6)
B	43	64.4 (±9.6)	57.6 (±10.5)
C	35	60.9 (±9.9)	40.6 (±14.1)
D	42	30.0 (±8.6)	21.4 (±9.5)
Total	168	67.1 (±4.5)	51.0 (±4.5)

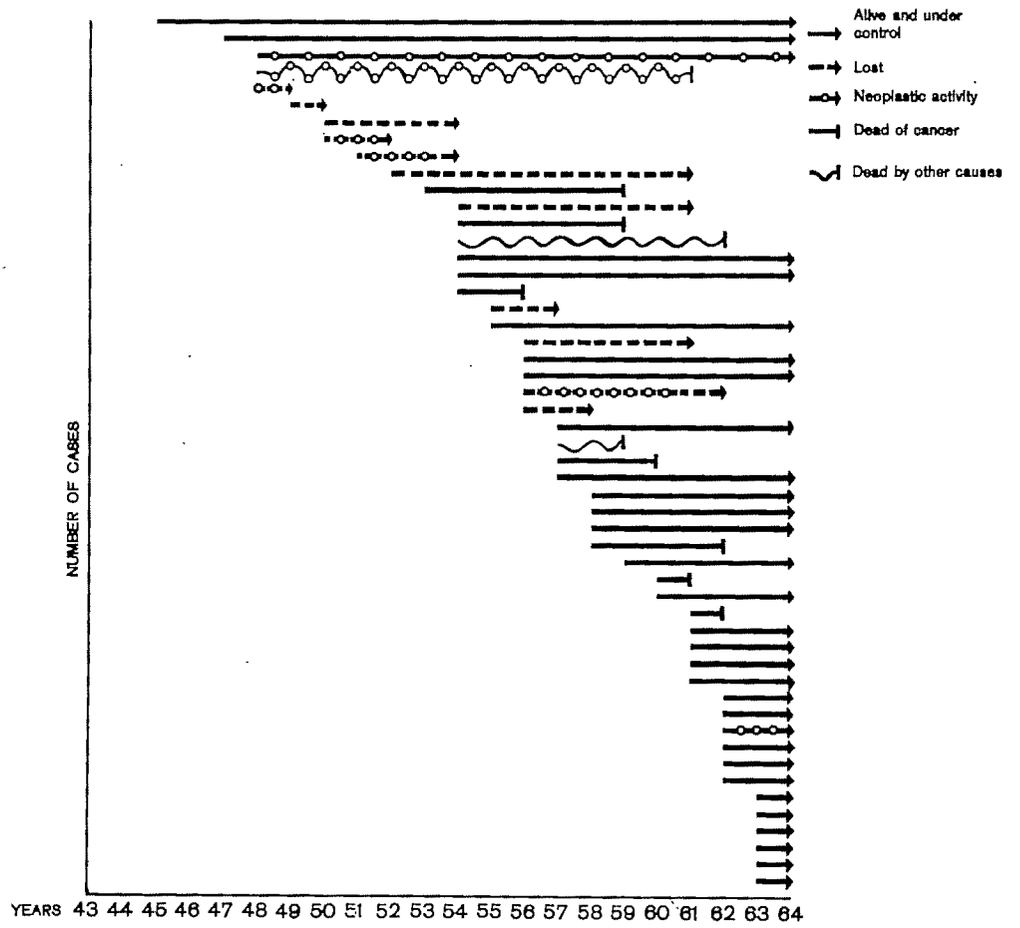


FIG. 5a. Survival diagram of patients in Stage B.

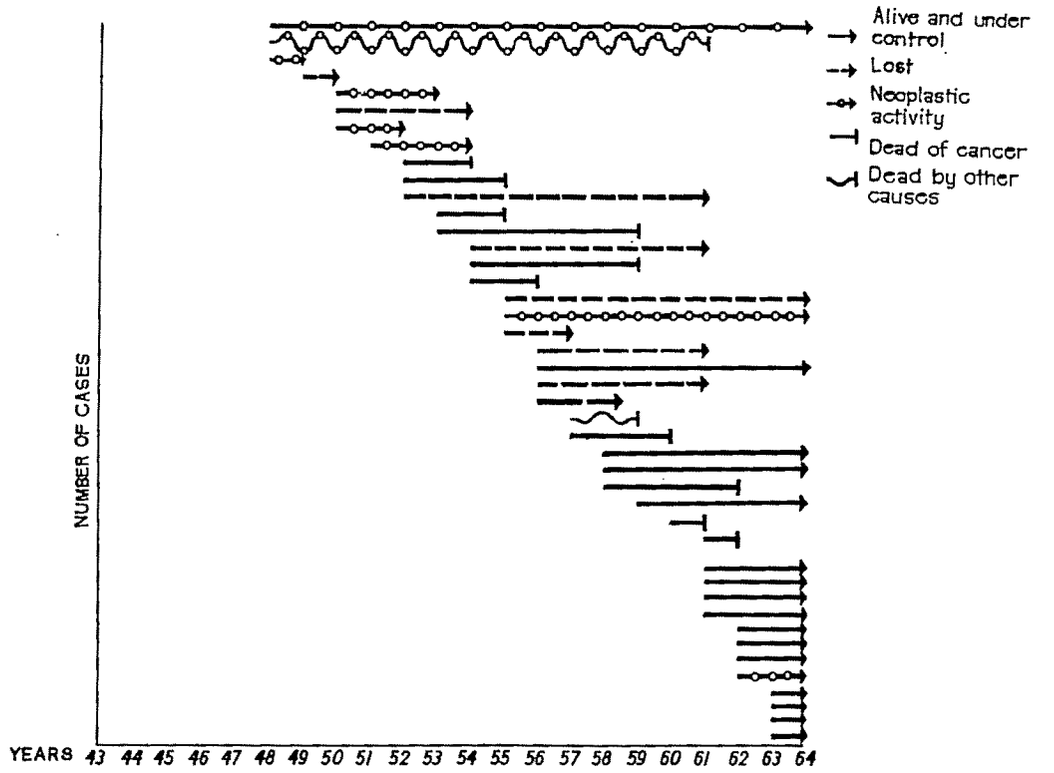


Fig. 5*b*. Survival diagram of 43 patients in Stage B, based on histopathologic study of the surgical specimen.

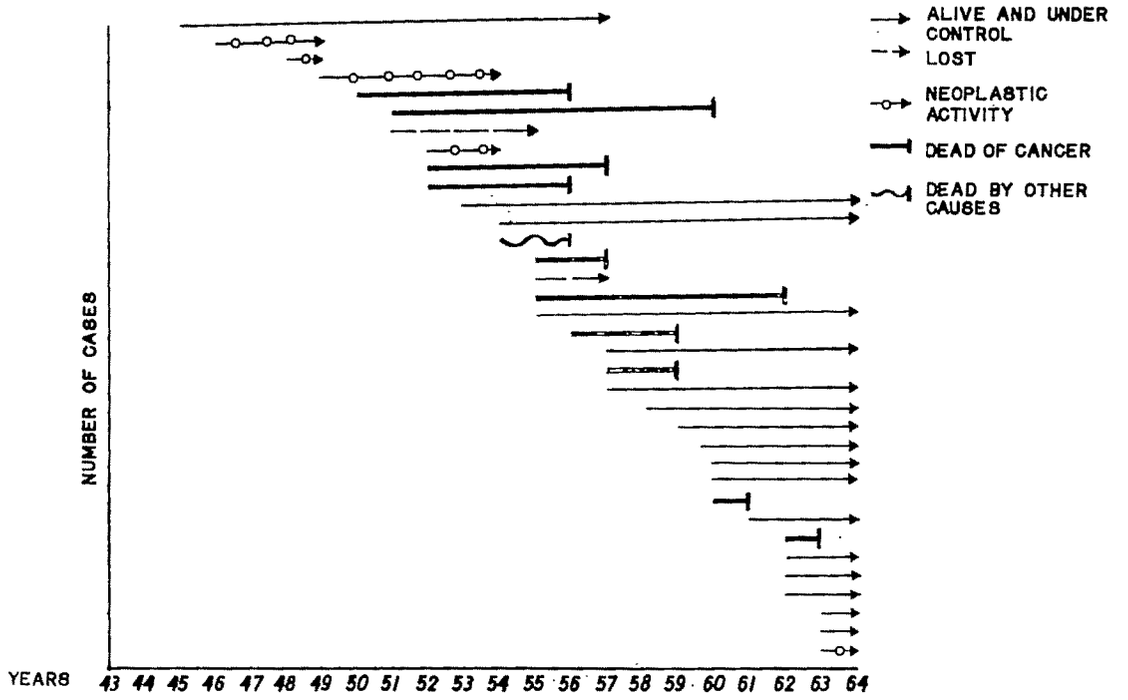


Fig. 6. Survival diagram of patients in Stage C.

Table XII shows a synthesis of the curability data. Our rates for curability are generally high, even if the magnitude of some of the standard errors broadens the values of the confidence intervals. However, in 8 patients the carcinoma was formed over Schimmelbusch's disease. Some other patients have been previously operated on for simple fibrocystic mastopathy and although this disease is not actually considered as premalignant, it may eventually produce an authentic carcinoma.

COEXISTENCE WITH PREGNANCY

According to the criteria used, pregnancy is not a surgical contraindication. Four of our patients were pregnant. One, in Stage A, was operated while in her second month of pregnancy. Five years after this operation, she developed carcinoma of the other breast and a radical mastectomy was done. She is alive and well 10 years after the first operation and 5 years after the second.

Another patient, also in Stage A, was operated in her fourth month of pregnancy and she is alive and well after 9 years.

The two other pregnant patients had Stage C and Stage D carcinomas, respectively. They received palliative radiation therapy only.

BILATERAL NON-SIMULTANEOUS CARCINOMAS

Our series contains 4 patients with carcinomas of both breasts. One, in Stage A, had carcinoma of the breast coexistent with pregnancy and developed carcinoma of the opposite breast 5 years later. Another, also in Stage A, was radically operated 6 years ago. Five years later she developed a carcinoma of the other breast. The suspicion that they were not independent from each

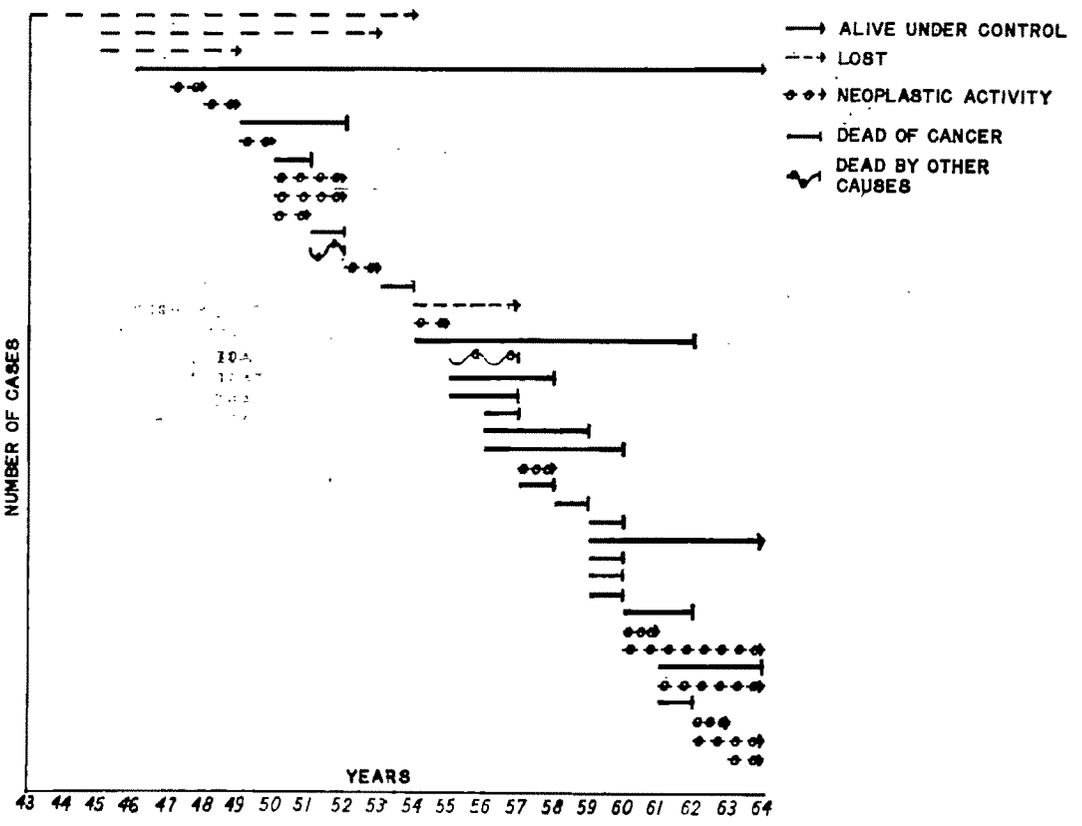


Fig. 7. Survival diagram of patients in Stage D.

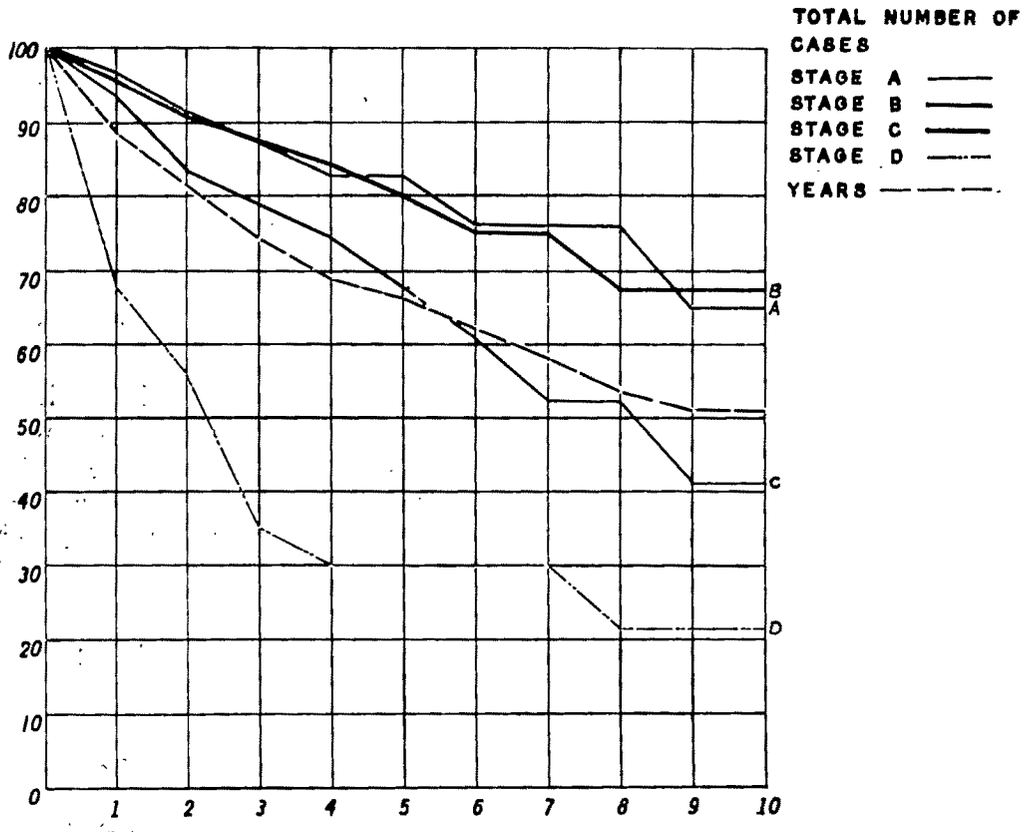


FIG. 8*a*. Survival curves according to Stages in 174 cases of breast cancer (actuarial analysis).

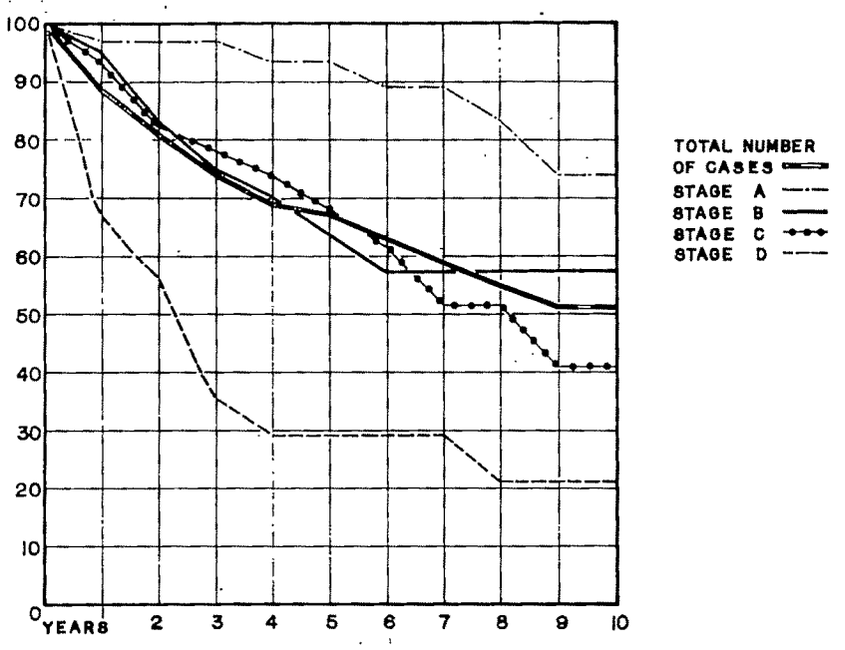


FIG. 8*b*. Survival curves (according to the actuarial analysis). Stages A and B have been determined on the basis of anatomopathologic study of the surgical specimen.

other led us to simple mastectomy followed by irradiation. No new activity has appeared after 10 months of the second treatment. The third case, in Stage C, had radical mastectomy 9 years ago, and simple mastectomy of the other breast 4 years ago, without apparent recurrence at this moment. In these last 2 cases, the second operation was simple mastectomy followed by irradiation, because we suspected that the second tumor was not an independent primary, and because of the fear that surgery might favor the spreading of the carcinoma. The fourth patient had cystosarcoma phylloides of the malignant variety. We performed a left radical mastectomy. A year later she presented the same disease on the right side. She is apparently well after 5 years of the first operation and 4 years after the second.

Finally, we mention that 3 of our patients with breast cancer later developed endometrial carcinoma.

PREOPERATIVE RADIATION THERAPY

Preoperative radiation therapy is given by us in those cases where we find surgical contraindications in the cancerologic sense, with the idea that if the cancer regresses sufficiently, the patient may be operated. Otherwise, radiation therapy is continued as the basic treatment. Figure 9 shows the survival diagram of 19 patients who were operated after preoperative irradiation. Because of the small number no definite conclusions can be drawn, but out of the 11 patients in Stage D, 4 lived 5 years or longer.

SUMMARY

We have described the rules by which the Department of Neoplastic Diseases of the Hospital Español, México, D.F., guides its diagnostic and integrated therapeutic approach to breast cancer.

Our therapeutic criteria are discussed. The obtained results are given.

It is not our intention to devise general methods or procedures; rather, our aim, based on a local work formula, is to give clinical coherence to the therapy of breast cancer.

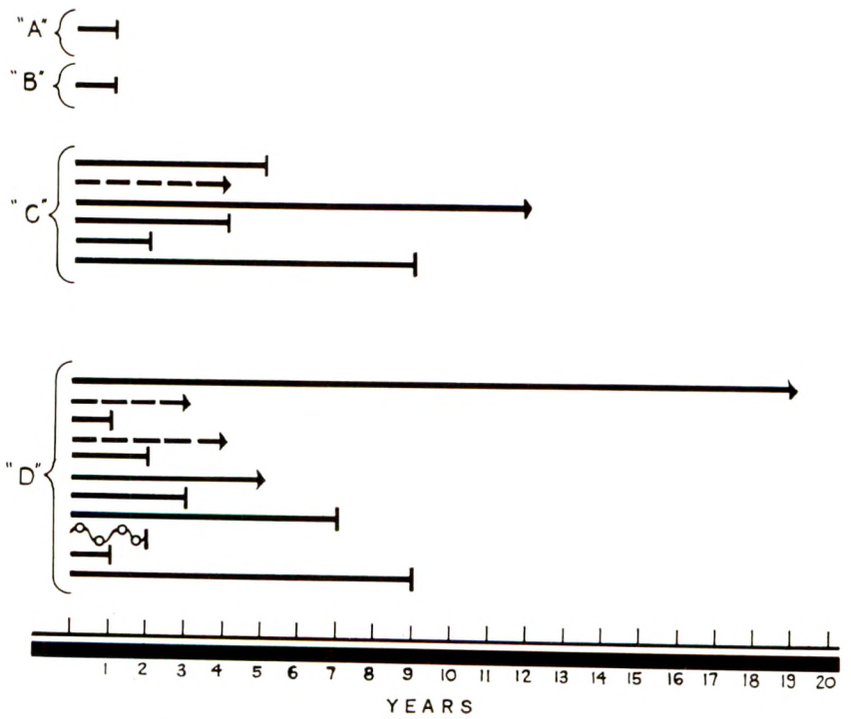


Fig. 9. Survival diagram of 19 patients who received preoperative irradiation.

In other words, we have tried to establish a Cancer Center in a General Hospital. We believe that the results obtained justify such an effort.

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DOES PROPHYLACTIC RADIATION THERAPY GIVEN FOR CANCER OF THE BREAST PREDISPOSE TO METASTASIS?*

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THE therapeutic value weighed against the possible harmful effects of prophylactic postmastectomy radiation therapy is continuously being discussed.

In 1962 Dao and Kovaric[4] reported a higher incidence of ipsilateral lung and skin metastases in patients who received postoperative radiation therapy following mastectomy than in those who had surgery alone. They noted ipsilateral lung metastasis in 30 per cent of 30 patients who were irradiated postoperatively and in only 5 per cent of 213 patients who received no irradiation. There were "skin metastases" in 47 per cent of the 30 patients receiving irradiation and 11 per cent of the 213 patients who received no irradiation. Based on these observations, the authors suggested that irradiation may increase the susceptibility to metastasis in the ipsilateral lung and chest wall.

The publication of Dao and Kovaric has caused concern and discussion among radiotherapists and surgeons. The purpose of this report is to analyze our material for further information on this subject.

MATERIAL

This study includes all of the clinic patients who had primary operable cancer of the breast and who were treated at the Breast Service and the Radiation Therapy Department of Memorial Hospital for Cancer and Allied Diseases during the years of 1950, 1951, 1953 and 1954. In the former 2 years nearly all the patients received no prophylactic radiation therapy; a few who had a particularly poor prognosis were excepted. In the latter 2 years, nearly all patients were irradiated postoperatively with few exceptions. This was part of a study to determine the influence of prophylactic radiation therapy on the patients' survival rate.

In order that a comparison could be made with the material studied by Dao and Kovaric, the following criteria were used. All patients must have had a primary infiltrating cancer of the breast treated by adequate surgery. Patients who had a separate cancer in other organs at any time were excluded.

During the years reviewed, there were 790 patients who had primary operable carcinoma of the breast. Of these, 116 were excluded for the following reasons: 6 had local excisions only, 8 had simple mastectomies, 4 had noninfiltrating cancer, and 98 had a second primary cancer, either previously, simultaneously, or within the subsequent 5 year observation period. The distribution of the second cancers was as follows: 59 in the opposite breast; 13 in the corpus or cervix uteri; 10 in the gastrointestinal tract; 6 in the ovaries; 4 in the head and neck; 3 were lymphomas; and 3 were in miscellaneous sites. There remained 674 patients for analysis.

Of the 674 patients, 205 received postoperative irradiation and 469 did not. In the irradiated group, 188 had radical mastectomy and 17 had an extended radical mastectomy as described by Urban and Baker.[8] Of the 469 patients who did not receive prophylactic irradiation, 442 had a radical mastectomy, and 27 had an ex-

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TABLE I

PRIMARY TREATMENT

(674 Patients)

	Post-operative Radiation Therapy	No Post-operative Radiation Therapy
Radical Mastectomy	188	442
Extended Radical Mastectomy	17	27
Total	205	469

tended radical mastectomy (Table I).

During these years, 250 kv. equipment was used for prophylactic irradiation. The routine was to treat the supraclavicular fossa, including the apex of the axilla, through opposing anterior and posterior fields, and the internal mammary area with one anterior field. The supraclavicular fields varied from 10 cm.×12 cm. to 13 cm.×16 cm. A midplane dose of 3,500 rads was delivered in 3 to 4 weeks. The internal mammary field was irradiated concurrently through one anterior field, averering 15 cm.× 7 cm., giving a tissue dose of 3,500 rads, calculated at 4 cm. depth. The average skin dose to each of the supraclavicular fields was 3,000 rads and to the internal mammary area, 4,500 rads. In those patients who had extended radical mastectomy with removal of the internal mammary lymph nodes, only the supraclavicular area was irradiated.

In 33 patients in whom lymphatic permeation of the skin of the breast was noted in the surgical specimen or who had very large primary lesions, the chest wall as well as the lymph node bearing areas were irradiated with the 3 field tangential technique.[1,5] On average, a 26 cm.×12 cm. medial and lateral opposing portal, both at 55 cm. target skin distance and a 16 cm.× 14 cm. supraclavicular portal at 50 cm. target skin distance were used. This treatment was planned to deliver a tissue dose, calculated at the intersection of the 3 beam axes, of 3,500 to 4,000 rads in 3 to 4 weeks.

Patients who received radiation therapy had more extensive disease. There were axillary lymph node metastases in 83 per cent of the irradiated patients and in only 46 per cent of the nonirradiated patients (Table II). Also, the patients selected for irradiation had higher levels of axillary lymph node metastases. There was involvement of the apex of the axilla in 52 per cent of the irradiated patients with positive axillary lymph nodes and only in 29 per cent of those who received no irradiation (Table III).

RESULTS

The results were first analyzed to compare the 5 year survival rates of the 2 groups of patients who did or did not receive postoperative irradiation (Table IV). When there was no axillary lymph node metastasis, the survival rates were 86 per cent (30/35) for the irradiated patients and 81 per cent (231/250) for the others. If the axillary lymph nodes contained metastases, the survival rates were 44 per cent (75/170) in the irradiated patients and 47 per cent (103/219) in those not irradiated. The total 5 year survival rates of the 205 patients who received irradiation and the 469 patients who received no irradiation were 51 per cent and 71 per cent, respectively. The data appeared to indicate that the 5 year survival rates of the patients with comparable stage of disease were similar and that the lower total survival rate of the irradiated patients reflects the fact that

TABLE II

OPERATIVE AXILLARY LYMPH NODE STATUS

Axillary Metastasis	Postoperative Radiation Therapy		No Postoperative Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Positive	170	83	219	46
Negative	35	17	250	54
Total	205	100	469	100

there were more patients with advanced disease in the irradiated group.

When the patients who had axillary lymph node metastases were divided according to the level of involvement, it was noted that the survival rates were similar in patients who had disease in the low and middle axillary levels (Table v). There was however, an increase of 17 per cent in the survival rate of the irradiated patients over the nonirradiated ones when the apical axillary lymph nodes were involved. This is statistically significant with a P value of 0.05.

The results were then analyzed to compare the incidence of recurrences and metastases which occurred within 5 years of the mastectomy. Lung metastasis occurred within 5 years of the mastectomy in 30 per cent (53/170) of the irradiated patients with positive axillary lymph nodes and in 25 per cent (53/219) of the others (Table vi). The incidence of ipsilateral lung metastasis was 6 per cent (11/170) in the irradiated patients with positive axillary lymph nodes, compared to 5 per cent (10/219) in the nonirradiated ones. The inci-

TABLE III

HIGHEST LEVEL OF AXILLARY METASTASIS

	Postoperative Radiation Therapy		No Postoperative Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Low Axilla	37	22	90	41
Mid Axilla	40	24	63	29
Apex of Axilla	89	52	63	29
Level Unknown	4	2	3	1
Total	170	100	219	100

TABLE IV

FIVE YEAR SURVIVAL RATE

	Postoperative Radiation Therapy			No Postoperative Radiation Therapy		
	Total No. of Patients	No. of Patients Survived	Per Cent	Total No. of Patients	No. of Patients Survived	Per Cent
Positive Axillary Lymph Nodes	170	75	44	219	103	47
Negative Axillary Lymph Nodes	35	30	86	250	231	81
Over-all	205	105	51	469	334	71

TABLE V

FIVE YEAR SURVIVAL RATE IN PATIENTS WITH AXILLARY LYMPH NODE METASTASIS

	Postoperative Radiation Therapy			No Postoperative Radiation Therapy		
	Total No. of Patients	No. of Patients Survived	Per Cent	Total No. of Patients	No. of Patients Survived	Per Cent
Low Axilla	37	23	62	90	57	63
Mid Axilla	40	15	38	63	29	46
Apex of Axilla	89	35	39	63	14	22
Level Unknown	4	2	—	3	3	—
Over-all	170	75	44	219	103	47

TABLE VI

INCIDENCE OF LUNG METASTASES WITHIN 5 YEARS

	Postoperative Radiation Therapy		No Postoperative Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Positive Axillary Lymph Nodes				
Ipsilateral	11	6	10	5
Contralateral	9	5	9	4
Bilateral	28	16	26	12
Undetermined	5	3	8	4
Total	53/170	30	53/219	25
Negative Axillary Lymph Nodes				
Ipsilateral	—	—	3	1
Contralateral	1	3	4	2
Bilateral	1	3	6	2
Undetermined	—	—	1	—
Total	2/35	6	14/250	5

dence of metastasis to the contralateral lung in the irradiated patients with positive axillary lymph nodes was 5 per cent (9/170) compared to 4 per cent (9/219) in the nonirradiated ones. Bilateral pulmonary metastases occurred most frequently in both groups, with 16 per cent (28/170) in the irradiated patients and 12 per cent (26/219) in the others. None of these differences is statistically significant. There was no ipsilateral pulmonary metastasis in the irradiated patients with negative axillary lymph nodes and in only 1 per cent of the nonirradiated ones (3/250). Contralateral metastasis occurred in 3 per cent (1/35) of the irradiated patients without axillary metastasis and in about 2 per cent (4/250) of the others. In this clinical setting bilateral metastases occurred in 3 per cent (1/35) of the irradiated patients and in about 2 per cent (6/250) of the nonirradiated ones. None of these differences is statistically significant.

Pleural effusion occurred in the ipsilateral side of the thorax in 12 per cent of the patients with positive axillary lymph nodes whether they were irradiated (21/170) or not (27/219) (Table VII). The incidence of contralateral and bilateral effusion in patients with positive axillary lymph nodes is also shown in Table VII. In the patients whose axillary lymph nodes contained no metastasis, ipsilateral effusion was present in 3 per cent (1/35) in the irradiated ones and 1 per cent (3/250) in those not irradiated. Contralateral effusion was noted in 3 per cent (1/35) of the irradiated group and in 2 per cent (6/250) of the nonirradiated group. Bilateral effusion occurred in only 1 nonirradiated patient with negative axillary lymph nodes and in none of the irradiated cases. None of the above differences is statistically significant.

The 5 year incidence of local recurrence in the skin of the chest wall was 24 per cent (42/170) in the irradiated patients who had positive axillary lymph nodes and in 23 per cent (50/219) of those not irradiated. In the irradiated patients, there was an almost equal incidence of skin metastasis inside or outside the radiation fields as shown in Table VIII. There was no local recurrence in the irradiated patients with negative axillary lymph nodes and in only 3 of the nonirradiated patients.

The incidence of recurrence in the internal mammary lymph nodes in the irradiated patients was 1 per cent and in the

TABLE VII

INCIDENCE OF PLEURAL EFFUSION WITHIN 5 YEARS

	Postoperative Radiation Therapy		No Postoperative Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Positive Axillary Lymph Nodes				
Ipsilateral	21	12	27	12
Contralateral	16	9	5	2
Bilateral	4	2	9	4
Undetermined	—	—	—	—
Total	41/170	23	41/219	18
Negative Axillary Lymph Nodes				
Ipsilateral	1	3	3	1
Contralateral	1	3	6	2
Bilateral	—	—	1	—
Undetermined	—	—	1	—
Total	2/35	6	11/250	3

nonirradiated patients it was the same.

The incidence of recurrence in the dissected axilla of the irradiated and nonirradiated patients was 4 per cent.

The rate of supraclavicular metastasis in the patients who had negative axillary lymph nodes at the time of surgery was 2 per cent (5/250) in the mastectomy only group, and none (0/35) in the irradiated group (Table IX). In the patients who had positive axillary lymph nodes at the time of surgery, the incidence of supraclavicular lymph node metastasis was significantly lower in those who received postoperative irradiation than in those who did not (17/170) or 10 per cent, *versus* 50/219 or 23 per cent) (Fig. 1). It is to be noted that the difference in the occurrence rate of supraclavicular metastasis was already evident at 1 year.

RADIATION COMPLICATIONS

The majority of the patients who received the 250 kv. irradiation with the

TABLE VIII

INCIDENCE OF LOCAL RECURRENCE IN SKIN OF CHEST WALL WITHIN 5 YEARS

	Postoperative Radiation Therapy		No Postoperative Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Positive Axillary Lymph Nodes				
Within Radiation Therapy Field	17	10	—	—
Within and Adjacent to Radiation Therapy Field	9	5	—	—
Outside Radiation Therapy Field	16	9	50	23
Total	42/170	24	50/219	23
Negative Axillary Lymph Nodes				
Within Radiation Therapy Field	—	—	—	—
Within and Adjacent to Radiation Therapy Field	—	—	—	—
Outside Radiation Therapy Field	—	—	3	1
Total	—	—	3/250	1

TABLE IX

INCIDENCE OF SUPRACLAVICULAR METASTASIS WITHIN 5 YEARS

	Postoperative Radiation Therapy		No Postoperative Radiation Therapy	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Positive Axillary Lymph Nodes	17/170	10	50/219	23
Negative Axillary Lymph Nodes	0/35	—	5/250	2

techniques described earlier had intense skin erythema at the end of the treatment. Areas of moist desquamation were observed frequently and usually subsided in about 2 weeks. These were particularly noticeable in the internal mammary portals where the skin dose was approximately 4,500 rads, delivered in 3 to 4 weeks. Dry desquamation, tanning, telangiectasia, and subcutaneous fibrosis were also common.

There were more serious complications in 10 patients (5 per cent). Of these, 6 had chronic ulceration of the skin (2 of which did not heal), 2 patients had chronic ulceration of the skin as well as radiation osteitis of the underlying bones, and 2 patients did not have skin ulceration, but did show radiation changes in the bones. Of the patients who showed evidence of radiation osteitis, there was 1 who developed pathologic fractures of the ribs and there was another who developed a pathologic fracture of the clavicle.

Approximately one-fourth of the patients who received postoperative radiation therapy were found to have apical pulmonary fibrosis on routine chest roentgenograms. This was usually minimal and asymptomatic. Only 4 patients had persistent pulmonary symptoms; cough in 2, cough and pain in 1, cough, pain and dyspnea in another.

DISCUSSION

As stated earlier, the purpose of this study was to analyze our material so as to gain further information on the therapeutic value and on the possible harmful effects of prophylactic radiation therapy. In particular, the study was made to evaluate the conclusion of Dao and Kovaric that radiation therapy predisposes to ipsilateral lung and skin metastases. If it could be proved beyond a doubt that routine prophylactic irradiation does not increase survival of patients with cancer of the breast, and if Dao and Kovaric's observation that such irradiation increases the incidence of lung and skin metastases were correct, and realizing that irradiation may damage normal tissues, then clearly prophylactic irradiation should be abandoned. The data in this study showed no evidence that irradiation favored the development of metastases, because if irradiation does predispose to metastasis, the incidence of ipsilateral lung metastasis in the irradiated patient should be greater than in the nonirradiated patient, and it also should be greater than in the contralateral lung of the same patient. Our data show that this is not the case. Furthermore, if irradiation

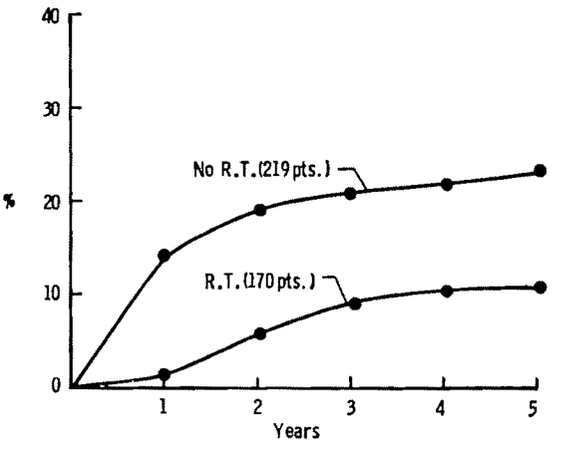


FIG. 1. Rate of supraclavicular metastasis in patients with positive axillary lymph nodes. R.T. = radiation therapy.

does predispose to metastasis, the incidence of pleural effusion in the ipsilateral side of the irradiated patient should be greater than in the ipsilateral side of the nonirradiated patient and it also should be greater than in the contralateral side of the same patient. Our data do not show this. If irradiation is to predispose to metastasis in the skin of the irradiated patient, the incidence of metastasis within the irradiation field should be higher than that outside of it in the same patient, and the total incidence of metastasis to the skin in the irradiated patients should be higher than that of comparable skin in the nonirradiated patients. Our data do not substantiate this. Thus, it can be stated conclusively that radiation therapy does not increase the probability of lung, pleural and skin metastases.

Even though no striking difference of the over-all survival rate between groups of patients who did or did not receive postoperative radiation therapy was found (either in a previous study using slightly different material[7] or in this study), there was some increase in the 5 year survival rate of patients who had metastatic lymph nodes in the apex of the axilla. Irradiation significantly delayed the development of and reduced the incidence of supraclavicular metastasis. Paterson and Russel[8] found delayed appearance of recurrence in the irradiated areas, although the survival rates of patients did not seem to differ in the groups of patients who received radiation therapy after radical mastectomy compared to patients who received it at the time of recurrence. Thus, it seems to us that further studies are needed before a final conclusion regarding the value of postoperative radiation therapy can be made, particularly in patients with metastatic lymph nodes high in the axilla. Perhaps supervoltage equipment should be used, since it can more safely deliver a higher dosage. Currently, we are investigating 2 mev. roentgen rays and high energy electron beams for postmastectomy prophylactic therapy.[2,3]

SUMMARY AND CONCLUSIONS

The results of 674 clinic patients with primary cancer of the breast who had radical or extended radical mastectomies, with or without postoperative radiation therapy at Memorial Center, were analyzed. There were 205 patients who received postoperative irradiation and 469 who did not.

Patients who received postoperative irradiation had more advanced disease as indicated by more frequent and more extensive axillary lymph node metastases.

Survival rates of the patients with the same stage of disease were similar except that there was a statistically significant higher survival rate at the 5 year level for the irradiated patients who had metastases in the apical axillary lymph nodes.

The incidence of lung, pleura and skin metastases was the same in the irradiated and nonirradiated patients who were compared according to their axillary lymph node status. Thus, Dao and Kovaric's observations that irradiation increases the probability of ipsilateral lung and skin metastases were not substantiated.

There was a lower incidence of and a delay in the appearance of metastatic lymph nodes in the prophylactically irradiated supraclavicular fossa.

Serious radiation complications consisting of chronic ulceration and/or radiation osteitis occurred in 10 of the 205 patients (5 per cent) who received orthovoltage postoperative radiation therapy.

Randomized studies with supervoltage equipment need to be done before the value of prophylactic radiation therapy for cancer of the breast can be accurately evaluated.

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PHYSICAL AND CLINICAL PARAMETERS IN THE MANAGEMENT OF ADVANCED BREAST CANCER WITH RADIATION THERAPY ALONE*

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IN A series of 1,336 patients with cancer of the breast without evidence of distant metastases on admission, seen between January, 1948, through December, 1963, 548 patients have had radiation therapy as their primary treatment. These patients had disease with the clinical features listed in Table 1. This presentation will deal with the following 3 major points: (1) comparison of local control in the protracted radiation therapy of Baclesse of 12 to 14 week treatment time with 250 kv., *versus* 8 to 10 weeks with cobalt 60; (2) estimating criteria for indication of simple mastectomy prior to radical radiation therapy; and (3) evaluation of a massive dose technique for tumors whose size and clinical features do not warrant the time and effort of a long protracted treatment.

Three other points will be discussed: the evaluation of need for "boost" therapy, *i.e.*, additional radiation to residual disease through limited field; the prognostic meaning of supraclavicular disease; and consequences of changing treatments from 5 to 3 days a week.

MEGAVOLTAGE VERSUS KILOVOLTAGE FOR PROTRACTED RADIATION THERAPY

When 4,000 to 5,000 rads are given in 4 to 6 weeks, 13 and 35 per cent local control of inoperable breast cancer is obtained.[1,8] In a series of patients with advanced breast cancer irradiated preoperatively with doses of 4,500 to 5,500 rads in 6 to 8 weeks, residual tumor was found in all specimens.[4] The only series [3,4,9] in which a significant percentage of local control and also long survivals have been obtained for patients with large inoperable masses are those in which therapy has been given with long protraction. Long protraction of treatment for breast cancer may be superior to a shorter period of treatment because vascularization improves as large masses shrink during treatment. There also may be a difference in the recovery factor of breast adenocarcinoma compared with squamous cell carcinoma.[5]

Irradiation performed with 250 kv., 3 mm. Cu half value layer, necessitates ultraprolonged treatment time. At the end of 12 weeks, the delivered skin dose to the anterior and posterior axillary portals is 4,800 rads (7,000 rads midaxillary tumor dose). Each tangential field receives, at the most, 4,800 rads air dose* (5,000–6,000 rads tumor dose to the primary lesion). Unless the palpable tumor in the corpus mammae and/or axilla has completely disappeared 2 and 3 weeks before completion of treatment, additional irradiation is given to the residual masses through reduced fields, bringing, in 14 to 15 weeks, the tumor dose to the primary lesion between 8,000 to 9,000 rads and to lymph nodes 7,500 to 8,000 rads.

With cobalt 60, the protraction becomes more flexible since skin tolerance is no longer a limiting factor. Because of the high probability of malignant cells infesting the dermal lymphatics in advanced tumors of the breast, a brisk erythema is still desirable and bolus is used for part of the treatment. Through the tangential fields, 6,000 rads tumor dose can be delivered (750 rads tumor dose per week) in 8 weeks without excessive skin reaction. A

* Air dose is used because the odd shape of the field does not permit an accurate determination of the skin dose.

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TABLE I

CLINICAL FEATURES OF ADVANCED TUMORS SUITABLE FOR RADIATION THERAPY ALONE OR PRECEDED BY SIMPLE MASTECTOMY

Initial Clinical Status	Initial Clinical Status, Greater Degree of Advancement
Primary < whole breast	Primary involves whole breast
Skin fixation, edema, ulceration <½ breast	Skin fixation, ulceration, over >½ breast
Satellite skin nodules in continuity with primary	Satellite skin nodules at periphery of breast
Pectoral muscle fixation	Chest wall fixation
Axillary lymph nodes multiple, high level, or semifixed	Massive fixed axillary lymph nodes
Inflammatory changes	Arm edema
Supraclavicular lymph nodes,* small, mobile	Large fixed supraclavicular lymph nodes
	Advanced age
	Poor medical condition

* Supraclavicular space is routinely treated as a regional lymph node site, not as distant metastasis.

given dose of 5,000 rads in 5 weeks is delivered to the anterior axillary portal and *q.s.* to the posterior axillary portal to make 5,000 rads tumor dose to the midaxilla. At 3 cm. depth the internal mammary chain receives 4,500 to 5,000 rads in 5 weeks. Additional irradiation to palpable disease brings the total tumor dose of 7,500 to 9,000 rads to the primary lesion in 65 to 70 days and 6,500 to 7,000 rads tumor dose to the axilla in 45 days.

Starting in 1954, the cobalt 60 unit has been increasingly used. The ulcerative and inflammatory lesions were still usually irradiated with kilovoltage since it was believed that the maximum skin dose delivered with kilovoltage would be a definite advantage. Before abandoning kilovoltage, a random study to include 50 patients was initiated in September, 1962, to determine if treatment time of 60 to 70 days with megavoltage would control local disease as

TABLE II

LOCAL RECURRENCES FOLLOWING PROTRACTED RADIATION THERAPY IN 50 RANDOMIZED PATIENTS

Location	250 kv. (12–14 weeks)	Cobalt 60 (8–10 weeks)
Breast	3 (1*)	1*
Supraclavicular	1*	—
Breast + Axilla	1	—
Breast + Supraclavicular	—	1
Breast, Axilla, + Supraclavicular	2 (2*)	1
Total	7 (4*)	3 (1*)
	Ulcerative tumors 5 Inflammatory tumors 8 Positive supraclavicular 4 Fixed to chest wall, pectoralis muscle, satellite nodules 8	Ulcerative tumors 2 Inflammatory tumors 5 Positive supraclavicular 3† Fixed to chest wall, pectoralis muscle, satellite nodules 16

* Inflammatory carcinoma.
† One patient with positive supraclavicular lymph nodes and inflammatory carcinoma.

well as 90 to 100 days with kilovoltage.

Twenty-five patients were treated with kilovoltage and 25 with cobalt 60. Table II lists the clinical characteristics of the primary tumors and the frequency and anatomic location of the recurrences. In spite of randomization, the 250 kv. series is weighted slightly with ulcerated and inflammatory tumors. There are 8 inflammatory tumors in the 250 kv. group and 5 in the cobalt 60 group. Four patients treated with kilovoltage had positive supraclavicular lymph nodes, while 3 were positive in the cobalt 60 series. Primary tumors were larger than 7 cm. in 20 patients, greater than 5 cm. in 12.

All patients now have at least a 2 year follow-up. In the kilovoltage group, 6 patients are free of disease, 3 are alive with distant metastases, 6 are dead from local disease and distant metastases, and 10 died from distant spread. The cobalt 60 group has 8 patients alive free of disease, 5 alive with distant metastases, 2 dead from local disease and distant metastases, 9 dead from distant metastases, and 1 dead of other primary cancer.

There were 7 local failures in the 25 patients of the kilovoltage group; 4 of these occurred in inflammatory tumors. There were 3 local recurrences in the 25 patients treated with cobalt 60, 1 occurring in an inflammatory carcinoma. In both groups, the breast was the most frequent site of recurrence. Two breast recurrences (1 in each group) were managed with simple mastectomy and both patients remained free of local disease, 1 until death at 3 years and the other is alive at 3 years.

Table III shows that the complications following these 2 treatment modalities are not significantly different except for major pneumonitis which developed in 3 patients in the 250 kv. group and was absent in the cobalt 60 series.

In summary, this randomized study shows no significant differences in local control in tumors treated by kilovoltage *versus* megavoltage techniques, even in ulcerative or inflammatory tumors. However, more than 5 to 6 weeks protraction is needed for large tumors. Two reasons are offered: long protraction permits continuing reduction of tumor mass with subsequent better oxygenation of tumor foci and also permits, because of limited tissue reactions, the delivery through reduced portals of additional 2,000 to 4,000 rads tumor dose in 10 to 20 days to residual masses. These doses, with higher daily rate (250 to 300 rads), are given at a biologically optimal time.

TABLE III

COMPLICATIONS OF PROTRACTED RADIATION THERAPY IN A RANDOMIZED SERIES OF 50 PATIENTS

No. of Patients	250 kv. 25	Cobalt 60 25
Necrosis of breast healed with conservative treatment <6 months	—	1
Unhealed at last follow-up or death	2	—
Minor pneumonitis	14	13
Major pneumonitis	3	—
Rib fracture	1	2
Limitation shoulder motion	—	2
Marked fibrosis	2	2

CLEANING SIMPLE MASTECTOMY PRIOR TO RADICAL RADIATION THERAPY

Large masses in pendulous breasts create a technical problem because of the difficulty of including the breast in the tangential fields. Furthermore, these large masses with or without ulceration, require enormous doses for local control because of the large number of tumor cells with probably a significant percentage of them hypoxic. A simple mastectomy prior to irradiation seems a logical solution to the problem, the treatment being then administered to a healed chest wall. This combination has produced better results than irradiation alone in Atkins and Horrigan's series.[1]

One hundred and ninety-six patients have had a simple mastectomy prior to radical radiation therapy, 25 patients

TABLE IV

LOCAL RECURRENCES IN PATIENTS HAVING HAD SIMPLE MASTECTOMY FOLLOWED BY RADICAL RADIATION THERAPY

Clinical Variety	No. of Patients	Chest Wall	Axilla	Supraclavicular Area	Chest Wall + Axilla	Chest Wall + Supraclavicular Area	Axilla + Supraclavicular Area	Chest Wall Axilla + Supraclavicular Area	Total
Ulcerative tumors	33	6	3	—	3	—	1	—	13/33 (39%)
Inflammatory tumors	13	1	—	—	—	—	1	1	3/13 (23%)
Others	150	8	6	4	3	2	3	1	27/150 (18%)
Totals	196	15	9	4	6	2	5	2	43/196 (22%)

before admission and 171 patients in order to facilitate treatment. These 171 patients were unsuitable for primary radical mastectomy because of skin and pectoral fascia fixation, peau d'orange, satellite nodules, chest wall fixation, and ulcerative (33 cases), and inflammatory (13 cases) cancers. Sixty-eight tumors were larger than 7 cm. Although the primary purpose of simple mastectomy prior to radical radiation therapy was to remove large or ulcerated lesions in pendulous breasts, rigid criteria were not used. A study of these cases was made to define criteria warranting simple mastectomy prior to radical radiation therapy.

Table IV shows the local recurrences after simple mastectomy and radical radiation therapy. In the entire group of 196 patients, 43 local recurrences developed; 15 recurrences on the chest wall alone and 10 on the chest wall plus the axilla and/or the supraclavicular area. Local control is poorest in the ulcerative tumors.

There is direct correlation between the degree of axillary involvement and axillary recurrence. Twenty axillary recurrences developed in 7 of 12 patients with axillary lymph nodes over 5 cm. in size, fixed to either skin or underlying structures and in 13 of 54 patients with multiple lymph nodes ranging from 2 to 5 cm. in size.

In summary, simple mastectomy followed by radical radiation therapy is locally more successful for large masses in pendulous breasts, without ulceration or massive axillary lymph node involvement. Ulcerative tumors which have large areas of skin and dermal lymphatic involvement show a trend toward greater recurrence with simple mastectomy (13 of 33 ulcerative tumors recurred) in comparison to a similar group of patients treated with protracted irradiation alone (16 of 55 ulcerative tumors recurred). The number of inflammatory carcinomas in this series is small; although recurrences developed in only 3 of 13 patients, there does not appear to be any advantage in treating these tumors with combined simple mastectomy and irradiation.

RAPID MASSIVE DOSE TECHNIQUE FOR PALLIATION OF FAR ADVANCED LOCAL DISEASE

A review of the 514 patients managed with radical radiation therapy with or without simple mastectomy shows that the presence of massive tumors (second Column of Table I) augurs very poor prognosis for survival. A need exists for rapid palliative treatment which can be accomplished without the time and effort required for long protracted irradiation.

Several authors[2,6,10] have indicated that local control of tumor can be achieved in a

high percentage of patients with massive doses given in a few fractions, but often at the expense of severe radiation complications in those patients who survive for some length of time. Of all treated patients reported by Edelman, Holtz, and Powers,[6] 43 per cent developed frozen shoulders and almost half of these developed paresthesia and shoulder pain. Twenty-eight per cent developed radiation pneumonia and 26 per cent developed lymphedema. Atkins[2] also reported a high incidence of pulmonary and shoulder complications in addition to 4 cases of myelitis. Stoll,[10] however, reported 44 cases with no severe complication other than a single necrosis.

The technique[7] consists of tangential fields covering the breast (including the internal mammary chain), supraclavicular fields including the supraclavicular space and axilla, and posterior axillary fields over the axilla only. The plan involves treatments on Tuesdays and Thursdays with a tangential field and the supraclavicular field treated on Tuesday, and the other tangential field and the posterior axillary field treated on Thursday. Each field receives 1,000 rads given dose. This same cycle of treatment is repeated 2 weeks later.

Our experience began with 4 patients treated with kilovoltage. There was complete control of growth in 1 patient; however, moist reaction continued intermittently for 9 months. The other 3 patients lived with unhealed skin necrosis for 2 to 8 months at which time they died from generalized disease. Therefore, no palliation was accomplished in this group of patients because of the severe discomfort due to local reactions.

Following this experience, all patients have been treated on the cobalt 60 unit where the treatment has been well tolerated. At first, 2,000 rads tumor dose also was delivered in 2 weeks. This was later increased to 3,000 rads in 3 weeks to palpable masses. In the intervening second treatment week, on Tuesdays and Thursdays, through reduced fields covering only the primary tumor, axilla, and if necessary the supraclavicular disease, additional radiation was delivered to bring the total tumor dose to approximately 3,000 rads. Recently, this has been increased to 3,500 rads tumor dose without early ill effects. Occasionally, bolus is used over skin nodules only in the second week with reduced fields.

TABLE V

SURVIVAL OF 34 PATIENTS WITH FAR ADVANCED LOCAL DISEASE WITHOUT INITIAL DISTANT METASTASES TREATED WITH COBALT 60 RAPID MASSIVE DOSE TECHNIQUE
(FOLLOW-UP 3 TO 36 MONTHS)

Time from Beginning of Treatment (mo.)	Dead
3	7
6	16
12	21
24	27
36	28

Two patients alive with no evidence of disease at 24 and 33 months.
Two patients alive with distant disease at 28 and 31 months.
Two patients alive with local and distant disease at 17 and 22 months.

Thirty-four patients have been treated by cobalt 60 rapid massive dose technique. Table v shows the survival periods of this group of patients.

All tumors involved the skin and varied from 8 to 15 cm. in diameter; 15 were fixed to the chest wall. Eleven patients had ulcerative carcinoma, and 9 patients had inflammatory carcinoma.

Response to radiation is arbitrarily divided into: poor—no growth restraint; good—regression of tumor with no further symptoms due to tumor for at least 8 months or for the remainder of life if shorter than 8 months but longer than 3 months; and excellent—disappearance of palpable disease for over 1 year or remainder of life if longer than 1 year. Table VI shows the response to treatment in 27 patients who survived more than 3 months. Of 9 cases of inflammatory carcinomas, 2 have had an excellent response but survival was limited to 11 and 12 months. Three had

TABLE VI

RESPONSE IN 27 PATIENTS TREATED WITH COBALT 60 RAPID MASSIVE DOSE TECHNIQUE

Dose	Excellent	Good	Poor
2,000 rads tumor dose	5	1	2
3,000 rads tumor dose (1,000 rads "boost")	6	5	4
>3,000 rads tumor dose (1,000–1,500 rads "boost")	2	1	1
Total	13	7	7

Seven patients died of metastatic disease in less than 3 months following irradiation and are excluded from evaluation.

good response; 4 were poor. There are 2 survivors who are free of diseases while in 32 of the treated patients, distant metastasis was the cause of death in addition to local disease in that group of patients which were poorly controlled with the palliative technique.

The complications were 6 necroses in the breast, 6 minor pneumonitis, 1 major pneumonitis, and 2 rib fractures. All necroses developed in primaries which had ulcerated skin; of the 11 ulcerative primaries, necrosis developed in over half. One can surmise that following massive dose therapy, melted tumor tissue cannot be replaced by granulation tissue and scar as occurs in protracted radiation therapy.

"BOOST" THERAPY

"Boost" therapy is the additional radiation given through limited fields to residual disease towards the end of treatment. Unless palpable tumor in the breast and/or axilla has completely disappeared 2 to 3 weeks before completion of treatment, additional therapy has been routinely given. In 1962, a random study began to include patients whose disease had disappeared by the ninth week (250 kv.) or the sixth week (cobalt 60). These patients were randomized to "boost" or "no boost." In the 50 patients treated with radical protracted irradiation, 7 patients in the 250 kv. group (3 with inflammatory disease) and 6 patients in the cobalt 60 series (2 inflammatory tumors) were included in the study. The 3 inflammatory tumors in the 250 kv. randomized to "no boost" recurred. In the 4 randomized to "boost," no recurrence has developed. In the cobalt 60 series, 1 patient with an inflammatory tumor was classed "no boost" and the tumor recurred, while the second patient was "boosted" and the tumor did not recur. One other patient who was randomized to "no boost" and did not have an inflammatory carcinoma also developed a recurrence.

Although the numbers are small, it would seem that regression rate in inflammatory tumors is not a valid assessment of tumor response and, therefore, these tumors have been exluded from the random study which is continuing in other types of tumors.

PROGNOSTIC MEANING OF SUPRACLAVICULAR DISEASE

Homolateral supraclavicular disease is considered in our institution advanced local disease, and these patients have been treated radically. The question of whether patients with supraclavicular disease should be managed with radical radiation therapy or with palliative treatment often has been raised.

In the 514 patients treated with radical irradiation, with or without simple mas-

TABLE VII

LENGTH OF SURVIVAL IN 67 PATIENTS WITH INITIAL CLINICALLY PALPABLE SUPRACLAVICULAR LYMPH NODES TREATED WITH RADICAL RADIATION THERAPY WITH OR WITHOUT SIMPLE MASTECTOMY (24 MONTHS MINIMUM FOLLOW-UP)

Time from Beginning of Treatment (mo.)	Dead
12	27
24	46
36	53
48	57
60	58
>60	61

Three patients died at 80, 89, 108 months of generalized cancer.
Six patients alive with no evidence of disease at 25, 37, 40, 45, 55, 74 months.

tectomy, 67 had clinically palpable positive supraclavicular lymph nodes (24 patients had positive biopsies) prior to treatment. (Of 67 patients, 22 developed local recurrences.)

Table VII shows the survival of the total of 67 patients with initial positive supraclavicular disease. Although 46 patients were dead within 2 years, 6 patients were free of disease from 25 to 74 months and 39 patients who died of distant spread had local control.

COMPARISON OF 3 VERSUS 5 DAY WEEKLY TREATMENT

In late 1962, in order to save megavoltage machine time, a trial of treatment administered 3 days per week instead of 5 days per week was initiated. The tumor dose remained unchanged; bolus was eliminated in the fourth and fifth weeks of the 3 day per week protracted treatment. Initially, patients were alternately chosen for either the 3 or 5 day week. Evaluation of acute reactions to treatment of 18 patients demonstrated no significant differences in local or general tissue tolerance in the 2 groups. Therefore, the 3 day treatment was adopted.

In the 3 day week, patients who were treated 2 to 3 years ago showed pronounced skin atrophy and telangiectasia and severe fibrosis. Shoulder movement restriction in face of the fibrosis had been averted only through intensive physiotherapy. Multiple radiation rib fractures were common.

Although the immediate reactions are not severe, it appears that the late sequelae will force a return to the 5 day week treatment.

SUMMARY

1. No significant differences in local control of advanced cancer of the breast have been demonstrated between kilovoltage (12 to 14 weeks) and cobalt 60 (8 to 10 weeks) radiation therapy.

2. Cleaning simple mastectomy followed by radical radiation therapy is indicated for large nonulcerated tumors in pendulous breasts without massive axillary involvement.

3. Few fraction massive dose radiation therapy is effective in the local control of far advanced tumors.

4. A study of "boost" therapy indicates that regression rate of inflammatory cancer is not a valid assessment of tumor response.

5. With palpable supraclavicular disease, more rigid criteria for the breast and axilla disease must be used to justify radical radiation therapy.

6. Late sequelae with the 3 day week treatments appear to be more severe than with the 5 day week treatments.

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MAMMOGRAPHY AND THE TRAINING PROGRAM OF THE AMERICAN COLLEGE OF RADIOLOGY*

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THE death rate from breast cancer has remained stationary for about the past 25 years, despite all efforts to reduce it. Breast cancer has retained its unenviable position as the Number 1 cancer killer of women. One out of every 19 American women will be affected by this disease. This seems almost unbelievable in this age of unlimited scientific achievements and the revolution in the biologic sciences that is unfolding an understanding of the growth processes. While surgery, and particularly radiation, have increased in efficiency during this period, they seem to have about reached their limits of usefulness. Hormone therapy has provided only occasional temporary regression of the disease, and while chemotherapy carries with it the inherent hope of a basic cure, it provides little more than a promise today.

The management of breast cancer had about come to a standstill when Egan[3] in 1960 published his experience with mammography at the M. D. Anderson Hospital and Tumor Institute on 1,000 patients. Mammography had been used before for studies of breast cancer, and had originally been performed by Salomon[11] in 1913. It was not until the 1950s that a serious attempt was made by Leborgne,[5] Gros and Sigrist,[6] Lame and Pendergrass,[7] and Lockwood[9] to develop it as a clinical diagnostic procedure. In the late 1950s Gershon-Cohen *et al.*[4] renewed interest in mammography, but without gaining widespread acceptance.

It remained for Egan to perfect a roentgenographic technique of diagnostic reliability that could be reproduced and utilized by radiologists. He emphasized that successful mammography depended upon obtaining roentgenograms of quality that could demonstrate small soft tissue tumors of at least 1.0 cm. in diameter and aggregates of microcalcific deposits within the breast. The roentgenographic technique required a special film and meticulous attention to the details of the exposure and development of the films—a technique so exacting that it requires special training for both the radiologist and the x-ray technologist, and a knowledge of the physiology and pathology of the breast.

After several years of clinical application, Egan and his associates, Dr. R. Lee Clark, Dr. Murray M. Copeland, and Dr. Gilbert Fletcher, brought their experience to the attention of Dr. Luther E. Terry, then Surgeon General of the United States Public Health Service, who subsequently sent 5 radiological consultants to study Egan's work and to advise him as to its merits. This group* was convinced that the Egan technique deserved further evaluation and recommended that a program be evolved under the joint cooperation of the Director of the National Cancer Institute, the Chief of the Cancer Control Branch and the Director of the M. D. Anderson Hospital for the evaluation of the reproducibility of the Egan mammographic technique by radiologists previously unfamiliar with it. This was done by formulating a protocol for 24 cooperating medical institutions, 10 in Texas and 14 throughout the country.

* These radiologists were: Thomas Carlile, M.D., Chief, Department of Radiology, Mason Clinic, Seattle; Eugene Pendergrass, M.D., then Professor of Radiology, University of Pennsylvania School of Medicine, Philadelphia; Wendell G. Scott, M.D., Professor of Clinical Radiology, Washington University School of Medicine, St. Louis; James Cooney, M.D., Vice-President for Medical Affairs, American Cancer Society, New York City; and Theodore Hilbish, M.D., then Chief, Diagnostic X-ray Department, Clinical Center, National Institutes of Health, Bethesda.

* Presented at the Forty-eighth Annual Meeting of the American Radium Society, Phoenix, Arizona, April 13–16, 1966.
† Professor of Clinical Radiology, Washington University School of Medicine, St. Louis, Missouri.

The results of this study were published in February, 1965,[1] and established that the technique of mammography as developed by Egan could be learned by other radiologists, that roentgenograms of acceptable quality could be produced, and that the interpretations provided information which was useful in the clinical management of breast disease. These studies also clearly confirmed that if mammography were to be successful radiologists and technologists would have to be trained in the technique and in the interpretation of mammograms.

To meet this situation an Ad Hoc Committee of the American College of Radiology was appointed to serve in an advisory capacity to the Cancer Control Branch, Division of Chronic Diseases, United States Public Health Service, which was then starting to make grants for the setting up of training centers for mammography. Under the Chairmanship of Dr. Arthur Present, the Ad Hoc Committee on February 7, 1965, convened a Standardization Conference on Mammography for the radiologists who had been working in mammography, the interested radiation physicists, and the representatives of the manufacturers of x-ray equipment and film. Their purpose was to determine what could be done to advance the technique of mammography through improvements in x-ray film and in x-ray equipment. They also recommended the development of a nationwide professional and technical training program for mammography, and that it be placed under the leadership of the American College of Radiology.

This recommendation was accepted by the College and in March of 1965, the President, Dr. Jackson Livesey, authorized the formation of the Committee on Mammography* within the Commission on Education and charged it with the responsibility to "study mammography as a practical diagnostic radiographic procedure and to determine the suitability and feasibility of having the American College of Radiology encourage professional education, training, and research in this procedure."

After considerable study, the Committee completed a report which was adopted at the Annual Meeting of the College in February, 1966. This report was unique in that it was the first time that the American College of Radiology was asked to approve a clinical diagnostic procedure; to formulate a national protocol for the training of radiologists and x-ray technologists in a diagnostic procedure; to prepare a program for the quality control of the procedure; to promote a standardization of a radiological and pathological nomenclature for an examination; and finally, to form a registry for eventually determining if mammography was contributing to a lowering of the death rate from breast cancer. The Committee arrived at these conclusions on the basis of the following developments in mammography.

That mammography had become the major factor in the roentgenologic detection of localized cancer of the breast prior to the development of axillary metastases; that it had encouraged the surgeon to undertake excisional biopsy examinations of nonpalpable lesions within the breast frequently resulting in finding unrecognized cancers; that it has been of significant assistance to the surgical pathologist in accurately locating a suspected area for the pathologic study of occult lesions within the breast; that no single procedure has done more in the last 5 years to renew interest and to advance the control of breast cancer; and that successful mammography requires teamwork by the radiologist, the surgeon, and the pathologist.

Furthermore, the roentgenologic diagnosis of malignant disease can be largely based on the detection of microcalcific deposits which are present in better than 70

* The members of the Committee are: Thomas Carlile, M.D., Murray M. Copeland, M.D., Robert L. Egan, M.D., J. Gershon-Cohen, M.D., Roger Harvey, M.D., Rudolph Kampmeier, M.D., Arthur J. Present, M.D., William Ross, M.D., Justin J. Stein, M.D., David Witten, M.D., David Wood, M.D., with Mr. Harvey Geller, Mr. Otha Linton, and Mr. William K. Melton as consultants.

per cent of all malignant tumors of the breast. With present day techniques, about 60 per cent of these will be shown to contain calcific deposits by mammography.

Radiologists must not only be familiar with the indications for mammography, but also with its limitations, because about 20 per cent of all cancers of the breast cannot be demonstrated by this examination, and about 10 per cent of the benign tumors of the breast will be over-read as cancer. Similarly, the detection of localized cancers by mammography is more difficult in women under 45 years of age (premenopausal women), but this is also true in the diagnosis of this disease by the clinician. For these reasons, the report of a negative mammogram does not give complete assurance that malignant disease is not present in the breast.

The Committee also felt that mammography had made other contributions to the control of breast cancer, namely:

1. That approximately 3 per cent of all patients with cancer of the breast when first seen by the clinician have simultaneous bilateral primary carcinomas of the breast. This is an important reason for making bilateral mammograms at the time when the patient is first seen.

2. That from 7.5 per cent to 10 per cent of all women[10] who have a breast cancer will have a second primary cancer in the contralateral breast. Therefore, the mammographic examination of the remaining breast at regular periodic intervals should prove to be very worthwhile in the early detection of such tumor.

3. The accuracy of the mammographic examinations is higher in postmenopausal women (55 years of age or older) and the accuracy is less in the premenopausal group (55 years of age or less).[3]

4. That since mammography can effectively demonstrate the gross features of certain benign conditions, such as ductal hyperplasia or papillomatosis, or other forms of fibrocystic disease, patients with these disorders should undergo repeated roentgenographic follow-up examinations to detect cancer in these groups of difficult patients before it is clinically evident and possibly in its incipient stage.

5. That localized cancers found by mammography alone are expected to have a much higher survival rate than cancers found by clinical examinations alone.

6. That already more patients are being found with earlier or localized malignant disease without axillary metastases.

7. That postoperative roentgenographic examination of the surgical biopsy or specimen is essential to determine: first, that the suspicious area has been excised by the surgeon, and, second, to assist the surgical pathologist in localizing the suspected area for pathologic studies. Pathologists who have been working with radiologists who are doing mammography agree that they are now looking at tissues much more carefully than ever before and are finding more localized lesions.

8. That mammography permits the opportunity to study breast cancers and their progress while the patient is undergoing hormonal or chemotherapy in cases not suitable for operative procedures.

9. That mammography at this stage should be confined primarily to symptomatic groups of patients. Only after wide competence has been developed among radiologists, should there be any significant effort in the direction of mass screening.

10. That preceptor instruction is the best way of training radiologists in mammography. Reading and demonstration materials, while helpful, are not sufficient.

With this report in mind, let us review the developments and what has been accomplished in the training program for mammography. First, there are now 11 centers in operation for the training of radiologists and technologists in mammography, covering almost all geographical areas in the continental United States and in Puerto Rico. Funds for their support come from the Cancer Control Branch, Division of Chronic Diseases, United States Public Health Service, on the basis of approved grants. Two more applications

are being processed. Those in operation are in the Departments of Radiology at:

1. Emory University School of Medicine, Atlanta, Georgia
2. M. D. Anderson Hospital and Tumor Institute, Houston, Texas
3. Mason Clinic, Seattle, Washington
4. Community Hospital, Glen Cove, Long Island, New York
5. Hutzel Hospital, Detroit, Michigan
6. Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania
7. Elmhurst Hospital, New York City
8. Presbyterian-St. Luke's Hospital, Chicago, Illinois
9. Mayo Clinic, Rochester, Minnesota
10. University of California School of Medicine, San Francisco, California
11. Gonzalez Oncologic Hospital, Puerto Rico

The average grant including investigation and accumulation of data is funded at $36,000.00 per year. Exclusive of the Emory project, the 10 other programs plan to train about 1,400 teams in 3 years at an average cost of $765 per team. To date, approximately 300 radiologists and about 200 technologists have received either the 3 or 5 day training course at these centers, and another 1,000 radiologists are doing mammography.

The principal trainees are practicing radiologists and residents in radiology for whom the 5 day training course is recommended. The training center reimburses the residents for travel and per diem expenses in accordance with accepted practice by the Cancer Control Branch. Radiologists are not reimbursed for travel or per diem expenses.

Application for radiological residents are made by the Chairman of the Department of Radiology directly to the training center and are acceptd in accordance with the available facilities as determined by the training center.

As part of the training program, it is recommended that the radiologist, resident or technologist return to the training center after an interval of from 2 to 3 months for a 3 day evaluation and refresher course.

Under special circumstances, certain residents in internal medicine, surgery, and pathology may also attend a training center as observers if facilities are available and the training center considers it desirable for furthering the mammography program in a particular hospital. Such arrangements must be requested by the chief of radiology of that hospital or institution. Residents other than those in radiology will not receive training in radiologic techniques.

Board certified radiologists may also apply at the centers for the training of designated technologists. However, technologists will not be accepted unless a radiologist from the same hospital or institution has taken or is in the process of taking the training course in mammography. Accepted technologists will be reimbursed for travel and per diem expenses in accordance with the training center's grant. It is desirable that technologists take their training during the same period as the radiologists.

The protocol for the operation of the training centers is actually a standard of minimum requirements to which the grantees agree to adhere at the time they accept the grant. These requirements were developed by the Cancer Control Branch with the Committee on Mammography and are kept under review in the customary manner as required by the Public Health Service.

The program for the quality control of mammography at the training centers and for any radiologist trained in this procedure is carried out in two ways:

One, through the Annual Seminars on Mammography, the Fifth of which was held at Emory University School of Medicine on April 29–30, 1966. At these 2 day meetings, the training centers report on their progress and discuss their achievements and difficulties. In this way they can receive help and suggestions from the other participants, from the members of the

Committee on Mammography, and from the invited consultants. These are organized, but informal meetings also provide an opportunity for the review of their roentgenograms and techniques.

The second, and perhaps an even more exacting factor in quality control, is Dr. Robert Egan, who continues to give his time and efforts to anyone who seeks his advice, and by the constant stream of communications that flows between him and each center.

The development of a satisfactory nomenclature for the uniform reporting of breast diseases as seen on the mammograms has been a more difficult process. The training centers have been using a preliminary classification that was prepared by Egan. A Subcommittee on Nomenclature and Classification with David M. Witten, M.D., as chairman has been studying this problem and will make their initial report at the next Seminar on Mammography. The membership of this committee includes radiologists, pathologists, and surgeons, who are also members of the Task Force on Breast Diseases of the American Joint Committee on the Clinical Classifications of Cancer for End Results Reporting and the Ad Hoc Breast Cancer Committee of the Cancer Control Branch of the Public Health Service for the correlation of information and cross-fertilization of ideas.

A Registry for Clinically Unsuspected Breast Cancers has been in operation at the Emory University Project for several years, but it is now proposed to formalize and to expand it. A Subcommittee headed by Robert Egan, M.D., is working on the plans. This is an extensive undertaking for it involves a definition of clinically unsuspected cancer; a categorization for the different types; the preparation of suitable forms for clinical, roentgenographic, histopathologic and follow-up reports—all suitable for IBM card coding. The repository for all records, mammograms and tissue studies from all the participating centers will be maintained at Emory University. Follow-up studies will be obtained at varying intervals dictated by the findings in each case, but never at intervals greater than 1 year. The study will be designed to continue indefinitely, will be periodically evaluated, and at 5 years a decision shall be made to continue or terminate the Registry.

The group of suspicious lesions reported by mammography and included in the Registry will be studied and followed in an attempt to develop criteria for the earlier diagnosis of cancer by mammography, to differentiate more accurately obscure breast calcifications and their significance, and to determine the possible relationship of intraductal hyperplasia, intraductal papillomatosis, intraductal carcinoma *in situ*, intracystic papilloma, and fibrocystic disease as related to cancer of the breast.

The latest projects of the Committee are the preparation of two surveys. The first, to be carried out by the training center at Emory University, is designed to give the Cancer Control Branch a measure of the usefulness and effectiveness of the various teaching materials which were organized by Egan and underwritten by the Cancer Control Branch in the teaching of mammography and also to obtain suggestions for improvements and methods of distribution.

The second survey is to obtain a more accurate number of the radiologists who are doing mammography, a description of their training in this procedure and where obtained, and an estimate of the existing demand for training by radiologists who are not now doing mammography.

Both of these surveys are being prepared by Mr. Harvey Geller, biostatistician in the Cancer Control Branch, for approval by the Committee on Mammography. These surveys will be mailed to all radiologists in the immediate future.

The last project of the Committee is in assisting the American Society of X-ray Technologists to form their own committee on mammography to stimulate their interest in and to promote their desire to

obtain formalized training at one of the training centers. Actually, the technologists have not shown the interest in attending the training centers that had been anticipated. This is disappointing since it is acknowledged that the success of mammography depends more on the technical quality of the roentgenograms than on any other single factor.

Finally, I would like to comment briefly on reports that are beginning to appear on surveys of mammographic examinations on rather large segments of the female population that have promising overtones.

Griesbach and Eads[5] at the Permanente Medical Group in San Francisco, California, have screened 12,245 women going through their health facilities and are diagnosing about 1.5 cases of breast cancer per 1,000 women having mammograms.

In April, 1965, Wolfe[13] reported his experience at the Yates Cancer Detection Clinic on 3,891 women, 46 years of age or older and asymptomatic as to breast disease, who had mammograms. He found 16 carcinomas of the breast, 14 of which had no evidence of axillary metastases at time of mastectomy, a rate of 4.1 per 1,000 women.

In the study on "Cooperative Evaluation of Mammography in 7 Teaching Hospitals"[8] done in Philadelphia, Pennsylvania, on 2,022 women between the ages of 30 and 60, a yield of 6 unsuspected carcinomas per 1,000 women subjected to routine mammography is reported.

Shapiro, Strax and Venet[12] in a preliminary study reported on the "Evaluation of Periodic Breast Cancer Screening with Mammography," in the *Journal of the American Medical Association* for February 28, 1966. This is an ongoing study on women 40 to 64 years of age who were enrolled in the Health Insurance Plan of Greater New York. In 9,883 women screened, they found 23 carcinomas, or a rate of 2.3 per 1,000 women screened, compared to a rate of 1.2 to 1.4 as the general incidence among women in Connecticut and upstate New York and in the Ten Cities Study respectively.

The reports of these surveys give some idea of the promise that the future holds for mammography. Our concern is that the procedure will be used prematurely by untrained groups and will again be discarded. This must be guarded against, and it explains why the American College of Radiology has become involved with this training program.

CONCLUSION

1. The American College of Radiology with the Cancer Control Branch of the United States Public Health Service has developed an extensive and practical program for training in mammography with built-in quality controls.

2. This program may well be the prototype for training in other diagnostic procedures in radiation therapy.

3. The ultimate goal of adapting mammography to large surveys of at least high risk groups of women is nearing practicality as the high risk groups are being better defined, more radiologists are being trained in mammography, and as the surgeons and pathologists are coming to the realization that successful mammography requires their participation on the team.

4. Mammography is not just the taking and reporting of roentgenograms of the breast, but is a procedure involving the cooperation of the radiologist, the pathologist, and the surgeon that gives it the promise of adding to the control of breast cancer.

5. Mammography may well be the stimulus that will lead to a better understanding of the natural history of breast cancer and may also provide us with a more satisfactory nomenclature for radiologic reporting and the pathologic classification of diseases of the breast.

6. The developments in thermography and xeroradiography are to be encouraged in organized programs, either separately or in cooperative projects, since all procedures have the same objective—the control of breast cancer.

7. Mammography is here to stay and, with continued refinements in the technique and further improvements in the films and x-ray equipment, it will become a routine radiological procedure in the management of breast cancer.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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Forty-ninth Annual Meeting: Royal York Hotel, Toronto, Ontario, Canada, May 29–31, 1967.

EDITORIALS

THE IMPORTANCE OF X-RAY MICROCALCIFICATIONS IN BREAST CANCER

STUDIES of the intact breast *in vivo*, no matter what technique is chosen or how fine the grain of the X-ray film, will reveal calcifications in only about 35 per cent of breast cancers. Nevertheless, demonstration of microcalcifications has importance in the X-ray diagnosis of breast cancer, often when the lesions are small and not yet palpable. Such lesions may be entirely unsuspected clinically because of the absence of symptoms or because the cancer is hidden in a mass of dysplastic glandular tissue.

Unfortunately, microcalcifications are also found in benign masses, such as proliferative epithelial hyperplasia, adenosis (especially of the dense sclerotic type), duct ectasia, and papillomatosis. The radiologist is, therefore, challenged to make a differential diagnosis, and this is not always easy.

In cancer, the calcareous particles may be present in numbers as few as a half-dozen or in excess of hundreds. In many cases, the particles appear in aggregates or clusters, sometimes in a cancer which can be delineated, at other times in tissue which cannot be identified as cancerous. When the particles can be seen in a spiculated dense mass, the scirrhous nature of the cancer is easily recognized. Deposition of the particles in tissue not clearly visualized as malignant is usually confined to duct cell cancers. In this situation, the particles follow the course of the ducts as the malignant cells extend lengthwise within the ducts.

Occasionally, the particles may be seen spread throughout a wide area of the breast along the ducts and, at the same time, aggregated in a scirrhous localization. The illusion may thus be created that the scirrhous cancer is the primary tumor and that the microcalcifications seen elsewhere in the perifocal tissues mark the direction of lymphatic spread of the growth. In such cases, it is most likely that the primary site of the cancer arose in some duct cells which then spread through the ducts, finally invading tissue beyond the duct walls, evoking a scirrhous reaction due to the local fibrosing action of the host tissue. The particles of calcium in such distribution lead easily to the diagnosis of cancer, but when their number is few and the tumor cannot be seen, the diagnosis becomes more difficult. It then becomes important to differentiate the microcalcifications of cancer from those which occur in benign conditions.

The calcifications which occur in duct ectasia are limited to the ducts, rarely implicating the alveoli. But being sharply outlined and embedded in the duct wall, these calcifications tend to be tubular and quite uniform in density. If the calcifications are limited to short segments, the deposits may become oval or circular in shape, resembling pearls, and we have come to designate such deposits as epithelial pearls. The smaller the size of these circular deposits, the more difficult becomes the visualization of their radiolucent centers, so that the use of a magnifying glass becomes advisable. Even with the help of magnification, some of these deposits are so small that they appear to be solid. They then begin to approach the appearance of the particles seen in cancer. Duct ectasia, however, is usually bilateral and this fact helps to exclude malignancy.

In adenosis, especially since it sometimes

undergoes focal fibrous involution, particularly in the later stages when marked sclerosis occurs, minute calcium deposits may be seen in areas which have hyalinized or necrosed. These deposits are more apt to be widely scattered in a disorderly manner in dense tissue, and are usually recognizable by the radiologist as those of sclerosing adenosis. The differential diagnosis from cancer, therefore, may not be too difficult.

In the presence of proliferative epithelial hyperplasia, the abundant desquamated cells distending the ducts may not be normally phagocytized, and the microcalcifications which mark the end of degenerative involution may result in deposits simulating those of cancer. Especially is the similarity of the deposits striking in that they are distributed along the course of the ducts and, in addition, they have similar sizes, shapes, and lack of uniform densities. Since epithelial hyperplasias tend to be bilateral, appearance of microcalcifications in both breasts helps to differentiate them from those of cancer.

Papillomatosis also is not infrequently associated with the deposition of microcalcifications and these particles, too, may simulate those of cancer. Usually, the number of such particles in a papilloma is small, but even so, some cancers also may present but a small number. The history of bleeding from the nipple and demonstration of the papilloma by contrast injection may help in the diagnosis.

Finally, in some circumstances, even when one of the dysplasias which are associated with microcalcification is easily recognized, the presence of a cancer cannot be excluded when clusters, aggregates, or arborization of minute calcium particles are seen. In these instances, biopsy is mandatory. It then becomes necessary for the sake of establishing an accurate diagnosis for the roentgenologist to localize the microcalcifications to be resected by the surgeon and localized in tissue for examination by the pathologist. This can be done routinely in the operating suite in the presence of the surgeon and the pathologist.

Among the last 100 cases of breast cancer, we found microcalcifications in 34 and the diagnosis was made in 6 cases in which the lesion was unsuspected. In 5 of these cases, the roentgenographic diagnosis was based solely on the presence of clusters or arborizations of microcalcifications. In one case, there were only a half-dozen particles. All of the tumors containing microcalcifications were less than 1.5 cm. in diameter, and none was associated with axillary lymph node metastasis. The diagnostic importance of discovering these microcalcifications, therefore, becomes obvious.

We suspect that the incidence of 5 per cent unsuspected cancers with microcalcifications that we encountered is lower than the expectancy because so few women of cancer age without breast symptoms resort to periodic X-ray examinations.

In summary, microcalcifications can be demonstrated in about 35 per cent of breast cancers, and in 5 per cent or more, the cancers may be unsuspected. In most cases, the microcalcifications occurring in benign dysplasias can be differentiated from those which occur in cancer; but in some situations, where a malignant papilloma or a carcinoma *in situ* cannot be distinguished from an infiltrating duct cancer, biopsy is mandatory. In these cases it is important that the deposits be localized in the breast for the surgeon and in the resected tissue for the pathologist by additional roentgenographic examinations of the specimen.

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In Memoriam

GORDON PALMER McNEER, M.D.
1905–1967

GORDON PALMER McNEER, 61, a practicing surgeon and internationally recognized specialist in cancer, died on January 18, 1967 in Lake Alfred, Florida, after an illness of several months. At the time of his death, Dr. McNeer was an Attending Surgeon at Memorial Hospital for Cancer and Allied Diseases in New York City and the James Ewing Hospital of the City of New York and was Chief of the Gastric and Mixed Tumor Services of the Department of Surgery in both institutions.

Born in Fairbanks, Alaska, on November 24, 1905, he came to New York City as a schoolboy and attended the Choir School of the Cathedral of St. John the Divine. Following further schooling at Phillips Andover Academy he matriculated at Princeton and graduated with a B.A. degree there in 1927. In 1931 he received his M.D. degree from the University of Pennsylvania. Following internship and surgical residencies at Mercy Hospital in Pittsburgh and at the old Ruptured and Crippled Hospital in New York City, he began his long association with Memorial Hospital as a Fellow and Resident, and since 1936 as a member of the Attending Staff.

His life-long interest in cancer and in its treatment was intensified by his tutelage under the late James Ewing, Director of the old Memorial Hospital staff. Early in his career, Dr. McNeer was concerned with the diagnosis and treatment of cancer of the stomach and was one of the pioneers in the use of the flexible gastroscope in the diagnosis of this and other disorders of the stomach. His many contributions to the subject of gastric cancer culminated in collaboration with his friend and associate, Dr. George T. Pack, in the preparation of a text, *Cancer of the Stomach*, now in press.

In recent years while continuing his interest in the treatment of patients with gastric cancer, Dr. McNeer devoted himself to the review and analysis of malignant melanoma based on his extensive experience in the management of this form of cancer coupled with that of his colleagues at Memorial Hospital. His work in this area was recognized by the American Radium Society which awarded him the Janeway Medal and Lectureship in April of 1966.

During World War II, Dr. McNeer served as Chief of Surgery with the 14th Evacuation Hospital in Burma and was discharged with the rank of Lt. Colonel.

Author of some 60 scientific publications and member of many professional societies having to do with surgery and with cancer, Dr. McNeer is probably best remembered by thousands of grateful patients and families for his skill as a dedicated physician and his devotion to the comfort and welfare of his patients.

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VOL. 99, NO. 4

NEWS ITEMS

THE AMERICAN COLLEGE OF RADIOLOGY

The Forty-third Annual Meeting of the American College of Radiology was held at the Century Plaza Hotel, Los Angeles, California from Tuesday, January 31 to Saturday, February 4, 1967.

The following officers were elected: *President*, J. E. Miller, M.D., Dallas, Texas; *Vice-President*, Ted F. Leigh, M.D., Atlanta, Georgia; *Secretary-Treasurer*, Fay H. Squire, M.D., Chicago, Illinois (re-elected); and *Chairman, Board of Chancellors*, Joseph D. Calhoun, M.D., Little Rock, Arkansas.

On Wednesday evening the College had a joint dinner meeting with the Los Angeles Radiological Society at which William Pickering, Director of Jet Propulsion Laboratory, Pasadena, California, was the Guest Speaker.

The convocation ceremonies were held Thursday at 5:30 P.M., with Dr. Jackson E. Livesay, President of the American College of Radiology, presiding. The degree of Fellow of the College was conferred on 66 candidates and the degree of Associate Fellow on 4 candidates who had been approved by the Board of Chancellors and elected by the votes of the Fellows.

The degree of Honorary Fellow was bestowed on Dr. Herman E. Hilleboe, New York, New York and on Dr. Samuel Schorr, Tel-Aviv, Israel; and *in absentia* on Dr. Eric Samuel, Edinburgh, Scotland; Dr. Basil Strickland, London, England; Dr. Kempo Tsukamato, Chiba, Japan; and Dr. Adolph Zuppinger, Bern, Switzerland.

Gold Medals, the highest award of the American College of Radiology for "distinguished service to radiology" was presented by President Livesay assisted by Dr. Miller, Chairman of the Board of Chancellors, to Dr. Edwin Charles Ernst, Sr., and Dr. Traian Leucutia, Editor of this JOURNAL.

The Friday meeting was devoted to the agenda of the College and on Saturday the always stimulating Annual Conference of Teachers of Radiology took place.

Members and Fellows of the College then flew by chartered planes to Honolulu, Hawaii, where a joint Seminar was held with the Hawaiian Radiological Society at the Hawaiian Village Hotel from Monday, February 6 to Wednesday, February 8, 1967. Guest Speakers for this Seminar were: Drs. Juan A. del Regato, J. Scott Dunbar, Benjamin Felson, Gilbert H. Fletcher, Harold G. Jacobson, Richard H. Marshak, Juan M. Taveras, and Manuel Viamonte, Jr.

The Forty-fourth Annual Meeting of the American College of Radiology will be held at the Drake Hotel, Chicago, Illinois, February 6–10, 1968.

SOUTHERN RADIOLOGICAL CONFERENCE

At the Eleventh Annual Meeting of the Southern Radiological Conference at the Grand Hotel, Point Clear, Alabama, the following new officers were elected: *Chairman*, Dr. Byron G. Brogden, Chief, Diagnostic Division, Department of Radiology, Johns Hopkins University, Baltimore, Maryland; *Vice-Chairman*, Dr. Howard Barnhard, Chief, Department of Radiology, University of Arkansas School of Medicine, Little Rock, Arkansas; and *Secretary-Treasurer*, Dr. Marshall Eskridge, Mobile Infirmary, P. O. Box 4097, Mobile, Alabama 36604.

The Twelfth Annual Meeting will be held at the Grand Hotel, Point Clear, Alabama 36564, January 26, 27 and 28, 1968.

ARMED FORCES INSTITUTE OF PATHOLOGY

Course in Cardiovascular Pathology

The Cardiovascular Pathology Course will be held at the Armed Forces Institute

of Pathology, Washington, D. C., on May 1–5, 1967.

The course is intended for interested clinicians, radiologists, and pathologists. It will consist primarily of a series of lectures delivered by staff members and visiting doctors on both congenital and acquired heart diseases.

There is no fee for the course. Acceptances are limited to the first 300 applicants. A program will be furnished upon request.

Applications should be made through The Director, Armed Forces Institute of Pathology, Washington, D. C. 20305.

II SIMPOSIO INTERNAZIONALE SUL TRATTAMENTO REGIONALE DEI TUMORI

The II International Symposium on the Regional Treatment of Tumors, with the theme "The Present Role in the Local Use of Radioactive-Isotopes, Associated with Surgery, in the Treatment of Malignant Tumors" will be held in Rome, Italy, June 2–4, 1967.

The Symposium is co-sponsored by the Istituto Regina Elena per lo Studio e la Cura dei Tumori, in Rome, and the Istituto di Oncologia of the University in Torino, under the patronage of the Italian Ministry of Health and the auspices of the Italian Societies of Surgery, Radiology and Cancer. It will be presented by 39 authorities in the field of Surgery and Radiology from the principal Cancer Institutes of the world.

The program includes Panel Discussions on: History, surgical and radiotherapeutic considerations; dosimetry; techniques and results with intra-arterial administration; techniques and results with endolymphatic administration; techniques and results with interstitial implantation; perspective and future.

For further information, please contact the Secretary of the Symposium, Dr. C. Nervi, M.D., Istituto Regina Elena, Viale Regina Elena, 291, Rome, Italy.

INTERNATIONAL NUCLEAR MEDICINE SYMPOSIUM

An International Symposium on "Radioactive Isotopes in the Localization of Tumors" will be held at the Imperial College of Science and Technology, London, S.W. 7., September 25–27, 1967.

This meeting will include sessions on Instrumentation; Isotopes; and Clinical Aspects of Scanning and other Techniques for the Localization of Tumors. There will be invited reviews on selected topics.

Offers of papers on recent work should be submitted with an abstract as soon as possible.

A technical exhibition by leading manufacturers of nucleonic equipment will be held in the same building.

Visits to various centers will be arranged.

Further inquiries and offers of papers should be made to Dr. V. R. McCready, Royal Marsden Hospital, Sutton, Surrey, England.

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BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

RADIATION THERAPY OF TUMORS AND DISEASES OF THE NERVOUS SYSTEM. By Jean Bouchard, M.D., F.A.C.R., F.R.C.P.(C), Professor of Radiology, McGill University; Consultant in Radiation Therapy, Montreal Neurological Hospital; Chief, Department of Therapeutic Radiology, Royal Victoria Hospital, Montreal, Quebec, Canada. Cloth. Pp. 244, with some illustrations. Price, $10.50. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa., 1966.

Periodically, particularly in oncology, it is necessary to re-evaluate a specific therapeutic modality in relation to advances within that field and within allied diagnostic and therapeutic areas.

The monograph under consideration is a re-evaluation of the position of radiation therapy in the treatment of "Tumors and Diseases of the Central Nervous System." The author introduces the subject with a general evaluation of the behavior of the neoplastic process in relation to the confines of the skull and spinal canal. The peculiar dynamics of intracranial vascular and cerebral spinal fluid systems as influencing intracranial neoplastic behavior are discussed. Further and detailed examination of the effect of kilovoltage and megavoltage radiation on the central nervous system gives perspective to the disease and the therapy. This analysis reviews both animal and human experience in the light of past and current pathophysiologic investigations arriving at a concept of radiation tolerance.

This background introduces the author's series of 564 patients. These patients have been thoroughly investigated both pathologically and clinically for periods of 5 to 25 years following radiation used as the sole therapeutic agent or in combination with surgery. From this vast experience the author is in a unique position to offer indications and contraindications in the use of this therapy. A detailed analysis follows each histologic category of tumor. For each category the author discusses the position of radiation therapy in relation to surgery, the potential of irradiation as a sole therapeutic measure and the possible role of chemotherapy. The technical aspect is described in terms of dosage, treatment ports and radiation sources.

The effectiveness of radiation therapy is presented in terms of salvage rates over periods of 5 to 25 years. This presentation includes patients treated with a combination of irradiation and surgery and, where indicated, irradiation alone. Such procedure allows evaluation of therapeutic effect of radiation in retarding neoplastic growth as compared with surgery or combination therapy. The progressive effectiveness of radiation therapy is measured against previous reports of the results of surgery alone and/or earlier radiation techniques. The concept of salvage rate is given further meaning in terms of the quality of survival as a measure of patient recovery.

This technique of evaluation is applied to gliomatous, nongliomatous, pituitary brain stem, spinal cord and metastatic neoplasms. Special attention is directed to the treatment of neoplasms of childhood, particularly as related to potential effects of radiation on the developing central nervous system.

Aside from its importance as a monumental study in time, quality and quantity of evaluation, this monograph places the awesome entity of central nervous system neoplasia in perspective. The author presents data revealing that, for certain of these diseases, with careful and thoughtful treatment, salvage rates of 25 years can be obtained; and for those less amenable to therapy, successful management with objective and subjective improvement may be expected for periods of months to years. Indeed, a welcome report.

FREDERICK R. CUSHING, M.D.

RADIACIONES IONIZANTES: FUNDAMENTOS FISICOS, RADIOBIOLOGICOS Y USOS TERAPEUTICOS. First edition. By Severino Perez Modrego, M.D., Professor Radioactive Isotopes and Nuclear Medicine, University of Madrid; Director of the Center of Oncology and Nuclear Medicine of the Hospital de San Juan de Dios, Madrid; and Antonio Plata

Bedmar, M.D., Collaborator, Board of Nuclear Energy, Madrid. Published by Artes Graficas Langa y Compañia, Tahona de las Descalzas, 6 - Madrid, Spain.

This book is a major contribution to the development of radiation therapy and nuclear medicine in Spanish-speaking countries. Until recently, as Doctor W. J. Meredith mentions in the foreword of this book, most publications on radiation therapy physics and radiation therapy have been written in English. The publication of this book in the Spanish language is an important accomplishment.

The radiotherapist will find a great deal of help in the Physics Section of this book, which will also be of great value to the radiophysicist. The Section devoted to Clinical Radiotherapy, which deals mainly with cobalt 60 teletherapy and radioactive isotope therapeutic techniques, is very well conceived and written to help the practitioner in his daily work.

The student of radiotherapy will find that the chapters dedicated to Radiobiology will provide him with a basic knowledge sufficient to further his endeavor in the discipline of more specialized work.

Antonio Rodriguez-Antunez, M.D.

BOOKS RECEIVED

Essentials of Urography. By Anthony F. Lalli, M.D., Assistant Professor, Department of Radiology, University of Michigan Medical Center, Ann Arbor, Mich. Cloth. Pp. 150, with 170 illustrations. Price, $12.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1966.

Anticancer Agents. By Frances E. Knock, Ph.D., M.D., Assistant Attending Surgeon, Presbyterian-St. Luke's Hospital; Clinical Assistant Professor of Surgery, University of Illinois College of Medicine; Director, Knock Research Foundation, Chicago, Ill.; Staff Physician, Surgical Service, Veterans Administration Hospital, Hines, Ill.; Formerly, Organic Chemist and Consulting Chemist, Armour Research Foundation and Merck, Sharp and Dohme. Cloth. Pp. 272, with many illustrations. Price, $15.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1966.

Transthoracic Needle Biopsy. By Sven Dahlgren, M.D., Department of Pathology, Karolinska Institutet, Stockholm; and Björn Nordenström, M.D., Director, Department of Thoracic Radiology, Karolinska Sjukhuset, Stockholm. Cloth. Pp. 132, with many illustrations. Price, $12.50. Year Book Medical Publishers, Inc., 35 E. Wacker Drive, Chicago, Ill., 1967.

Radiological Hazards to Patients. Final Report of the Committee. Ministry of Health, Scottish Home and Health Department. Paper. Pp. 33, with some figures. Price, $.70. Sales Section, British Information Service, 845 Third Avenue, New York, N. Y., 1966.

Seventh Symposium, Neuroradiologicum; New York, September 21–25, 1964. Part I: Skull Examinations; Angiography. Paper. Pp. 630, with many illustrations. *Acta radiol.* (Diagnosis), Volume 5, 1966.

Die Herzkatheterisierung bei angeborenen und erworbenen Herzfehlern. By Prof. Dr. O. Bayer, Chefarzt der I. Med. Klinik, Städt. Krankenhaus Berlin-Moabit; Prof. Dr. F. Loogen, Direktor der Abteilung für Kardiologie, Universität Düsseldorf; Priv.-Doz. Dr. H. H. Wolter, Oberarzt an der Med. Universitätsklinik Heidelberg; with a foreword by Prof. Dr. F. Grosse-Brockhoff. Cloth. Pp. 316, with 265 illustrations. Price, DM 90.-. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1967.

Die biologischen Wirkungen kleiner Dosen Ionisierender Strahlung: Eine Literaturübersicht. By Dr. rer. nat. Günter Siegel, Oberassistent am Institut für medizinische Physik und Biophysik der Humboldt-Universität, Berlin. Paper. Pp. 87. Price, MDN 8.40. Veb Gustav Fischer Verlag, Absatzabteilung, 69 Jena, Villengang 2, 1966.

Cardiovascular Roentgenology: A Validated Program. By Charles M. Nice, Jr., M.D., Ph.D., Professor and Chairman, Department of Radiology, Tulane University School of Medicine; Director of Department of Diagnostic Radiology, Charity Hospital of Louisiana at New Orleans; Consultant to U.S.P.H.S. and V.A. Hospitals, New Orleans, and to Mobile General Hospital, Mobile, Ala. Paper. Pp. 272, with 98 illustrations. Price, $9.35. Hoeber Medical Division, Harper & Row, Publishers, 49 East 33rd Street, New York, N. Y., 1967.

The Pathology of Emphysema. By Lynne Reid, F.R.A.C.P., M.R.C.P., F.C.Path., Reader in Experimental Pathology, Institute of Diseases of the Chest, Brompton Hospital, London; Honorary Consultant in Experimental Pathology to Brompton Hospital. Cloth. Pp. 372, with 173 figures. Price, $13.50. Year Book Medical Publishers, Inc., 35 E. Wacker Drive, Chicago, Ill., 1967.

Cancer of the Head and Neck. Papers presented at the International Workshop on Cancer of the Head and Neck, New York City, May 10–14, 1965. Edited by John Conley, M.D., Clinical Professor of Otolaryngology, College of Physi-

cians & Surgeons, Columbia University; Attending Otolaryngologist and Chief of Head and Neck Service, Columbia Presbyterian Medical Center; Chief of Head and Neck and Facial Plastic Surgery Department, Pack Medical Group; Chief of Head and Neck Service and Attending Otolaryngologist, St. Vincent's Hospital. Cloth. Pp. 640, with many illustrations. Price, $30.00. Butterworth Inc., 7300 Pearl Street, Washington 14, D.C., 1967.

NEURO-OPHTHALMOLOGY. Volume III. Symposium of the University of Miami and the Bascom Palmer Eye Institute. Edited by J. Lawton Smith, M.D., Associate Professor of Ophthalmology; Associate Professor of Neurosurgery; and Assistant Professor of Neurology, University of Miami School of Medicine, Miami, Fla. Cloth. Pp. 350, with 200 illustrations. Price, $25.00. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo., 1967.

EINFÜHRUNG IN DIE RÖNTGENDIAGNOSTIK. By Prof. Dr. U. Cocchi, Zürich; and Prof. Dr. P. Thurn, Direktor des Institutes für Röntgenologie und Strahlenheilkunde der Universität, Bonn. Cloth. Pp. 378, with 484 illustrations. Price, DM 49.50. Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1967.

DER LUNGENRUNDHERD: KLINIK, KASUISTIK, PATHGENESE UND RÖNTGENOLOGISCHE DIFFERENTIALDIAGNOSE. By Prof. Dr. Wener Rübe, Chefarzt der Röntgen- und Radiumabteilung des Knappschafts-Krankenhauses Recklinghausen apl. Professor für Röntgenologie und Strahlenheilkunde an der Freien Universität Berlin; with a foreword by Prof. Dr. H. Oeser. Cloth. Pp. 132, with 114 illustrations. Price, DM 66.-. Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1967.

RADIATION PHYSICS IN RADIOLOGY. By R. Oliver, M.A., M.Sc., F.Inst.P., A.M.I.E., M.I. Biol., Chief Physicist, United Oxford Hospitals and Radiation Protection Officer, Oxford University. Cloth. Pp. 127, with 37 illustrations. Price, $4.50. F.A. Davis Company, 1914 Cherry Street, Philadelphia, Pa., 1966.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

Dugdale, L. M. Echo-encephalography: the use of pulsed ultrasound in neurological diagnosis. *Australasian Radiol.*, Aug., 1966, *10*, 207–216. (From: The Alfred Hospital, Melbourne, Australia.)

One of the most important objective findings in a patient with a suspected supratentorial intracranial lesion is the situation of the midline structures of the brain, principally the third ventricle, septum pellucidum and pineal gland. A shift of the midline structures to one side implies either (1) an atrophic or fibrotic lesion drawing the brain substance towards the side of the lesion, or (2) a space-occupying lesion, displacing the midline structures away from the side of the lesion.

In any case, the presence of a shift of the midline structures is a definite indication for further investigation of the patient.

It has long been accepted that the only simple means of assessment of the position of the midline structures are the visualization and measurement of the position of a calcified pineal gland or habenular commissure. Unfortunately these structures are sufficiently calcified to be radiologically definable in only about 55 per cent of adults, and in practically no children under 16 years of age. Echo-encephalography gives this information in virtually all cases.

The assessment of the lateral position of the midline structures is, at present, the major function of the technique of echo-encephalography. Other data are also obtainable, such as the width of the third ventricle, and, less reliably, the width of the lateral ventricles, and sometimes the presence of an echo from the surface of a sub- or extradural collection. These should be consistently sought for and may give valuable diagnostic leads.

It is important to realize that the method does not replace any of the orthodox examinations, but is strictly supplementary.

The physical basis and technique are described in detail.

The criteria of evaluation are:

(1) There must be a high group of echoes from the skull on the opposite side to the probe; this group should show at least 2, and often 3, peaks, separated by 4–10 mm. These peaks represent, in order, the inner table and outer table of the skull.

(2) The midline structures should give rise to a group of at least 3 echoes in a characteristic pattern. The distance between the outer two echoes of the triad corresponds to the septum pellucidum and third ventricle.

(3) A further criterion applicable to the pair of tracings obtained from both sides of the head is that the total of the distances from midline structures to the inner tables of the skull should equal the internal diameter of the skull. If, for instance, the total skull width on the tracing is (say) 8.5 units, and the total of the two hemispheres is 11 units, this obviously means that at least one of the so-called midline echoes has been wrongly identified.

These 3 criteria have been applied to the echo-encephalograms of a series of 200 consecutive cases examined. Of the 200 cases, in 8 it was too difficult to obtain a satisfactory tracing—an incidence of 4 per cent. It appears that widespread subarachnoid spaces and dilated sulci give rise to a multiplicity of confusing echoes, these being the major cause of the difficulties.

The position of the midline structures was confirmed in 118 cases, in 26 cases by the position of pineal calcification only, and in 92 cases by angiography or pneumoencephalography.

Of the 8 difficult cases, it was impossible to even guess the position of the midline in 2. Of the other 6, in 1 the shift was missed, and of the 5 proved normal, in 4 an abnormal echo-encephalogram was tentatively suggested. This emphasizes that all tracings which do not conform to the given criteria should be rejected.

In spite of many subdural collections the characteristic echo was found in only 4 cases.

The author points out that errors may be committed by neglecting the above basic criteria and by performing echo-encephalography at only one level on the skull. Also, atrophy can easily be confused with subdural collections.

A valuable aspect of echo-encephalography is that it can be used to follow up patients at frequent intervals, as the method is nontraumatic, has no inherent risk, and is relatively easy to carry out.—*Stephen N. Tager, M.D.*

Salzano, F. M., and Ebling, H. Cherubism in a Brazilian kindred. *Acta genet. med. et gemel.*, July, 1966, *15*, 296–301. (From: Departamento de Genetica, Instituto de Ciecias Naturais, Cadeira de Histologia, Faculdade de Odontologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.)

The authors investigated the kindred of two brothers with cherubism. The information obtained involved 7 generations and a total of 75 individuals. Twenty-three individuals with cherubism were examined.

A brief history of the origin of the name cherubism is given and the classic facial appearance is described. The roentgenographic appearance, the histologic features and the genic aspects are discussed.—*Richard P. Taylor, M.D.*

Rosenberg, Henry M. Laminagraphy: methods and application in oral diagnosis. *J. Am. Dent. A.*, Jan., 1967, *74*, 88–96. (From: Department of Radiology, University of Illinois

College of Dentistry, 808 South Wood, Chicago, Ill.)

Body section roentgenography was initially and fundamentally developed to aid in chest evaluation in medical diagnosis. In the 1930s several investigators in different countries produced variations of this procedure termed planigrams, tomograms, stratigrams, and laminagrams.

In recent years this technique has been adapted for use in oral surgery diagnosis and especially for examination of the temporomandibular joints. One such instrument for this is called an ordograph.

The author gives detailed instructions and illustrations for obtaining the anteroposterior cephalometric laminagrams, the subzygomatic view using conventional roentgenography, and corrected lateral cephalometric laminograms of each condyle.—*Arch H. Hall, M.D.*

Neck and Chest

Simon, G. Radiology in epidemiological studies and some therapeutic trials. *Brit. M. J.*, Aug. 27, 1966, *2*, 491–494. (Address: Radiologist, X-Ray Department, St. Bartholomew's Hospital and Brompton, London, England.)

The author concentrates first on radiology in therapeutic trials of drug combinations in pulmonary tuberculosis, and secondly on radiology in epidemiologic studies of chronic bronchitis and emphysema and its value in the prognosis of these conditions.

Radiography would be useless to show the incidence of chronic bronchitis, since no abnormalities appear in the roentgenogram.

In most epidemiologic surveys or therapeutic trials only a single anterior-view roentgenogram is taken. Such a simple technique has its limitations. More elaborate roentgenographic techniques, such as tomography for the proof or exclusion of cavities, are usually impracticable in large-scale surveys, due to cost of equipment and expense.

The radiologic method is often attacked because of its inaccuracy and observer error. Observer error can be greatly reduced if measurable data, or even what is seen, are recorded on a prescribed form. Ideally this should be only for quantitative observations.

A form, as recommended by the Veterans Administration is advised, such as the *Classifications of Cavitation.*

Other data that might be of value are: the thickness of the cavity wall; the site of the cavity; whether the cavity lies within aerated lung, an area of consolidated lung, or in an atelectatic lobe.

An analysis of a number of cases recorded and grouped in this manner in an East African investigation (Dr. J. F. Heffernan, personal communication, 1966), suggests that cavities in atelectatic lobes are slower to disappear than others. Persistence of a cavity, therefore, may indicate a longer course of treatment than if the cavity resolves.

Considerable difficulty may arise in grading the severity of tuberculous lesions. The severity of the lung lesions as a whole can be gauged partly by the cavity grading, and partly by grading the anatomic extent of the disease itself.

A considerable confusion about roentgenologic diagnosis of emphysema exists. Accuracy of the roentgenologic diagnosis will be enhanced if the following criteria are strictly adhered to:

(1) *An excess of air in the lungs.* Roentgenologic evidence for this is a low flat diaphragm and a large retrosternal translucent area.

(2) *A narrow vertical heart;* a prominence of the pulmonary trunk; large hilar vessels with small lung vessels.

(3) *Bullae.* These appear as avascular transradiant areas which may be demarcated by a white line or may have no definite border.

On the basis of these roentgenologic criteria emphysema Grade III-IV, panacinar with air trapping, widespread throughout both lungs, will usually be diagnosed.

Lesser degrees of emphysema, and emphysema without air trapping, cause no such changes, and will therefore not be detected. Thus errors of observation can be separated from errors of conclusion.

For the purposes of assessment, particularly in regard to prognosis, widespread general emphysema with air trapping must be carefully distinguished from local avascular (bullous) areas, the rest of the lung being normal.

The roentgenogram is of little value in the grading of emphysema, except to indicate that it is widespread and severe.

Strange to say, nothing is known regarding which bronchitics develop widespread emphysema, why it occurs, or even accurately, when?

The mortality of those with the emphysema patterns was 53 per cent at 5 years.

The group with the large hilar but normal lung vessels and diaphragm can now be defined clinically and roentgenologically, and is therefore a suitable field for epidemiologic study. As yet the incidence of this complication among chronic bronchitics is not accurately known, nor is the prognosis at 5–10 years.

The incidence of right ventricular hypertrophy in those with the roentgenologic emphysema pattern is seen to be about the same at 17 per cent in cases where a postmortem examination has been made. The degree of hypertrophy was relatively slight.

A review of 400 cadmium workers failed to show a significant number with the emphysema pattern, although some had respiratory function studies indicating airways obstruction. A review of 400 coal miners seeking compensation was studied; the incidence of the roentgenographic emphysema pattern was small, but was higher in those with the lower

categories of nodulation. The author suggests that the focal emphysema of coal miners does not give rise to widespread emphysema with air trapping, and accounts for the difficulty found in trying to correlate the nodular shadows with disability.—*Stephen N. Tager, M.D.*

Stengel, Bruce F., Watson, Raymond R., and Darling, Ronald J. Pulmonary rheumatoid nodule with cavitation and chronic lipid effusion. *J.A.M.A.*, Dec. 19, 1966, *198*, 1263–1266. (Address: Dr. Stengel, Surgical Service, Veterans Administration Hospital, Wood, Wis. 53193)

Since 1947 over 50 cases of pulmonary rheumatoid disease in patients without known occupational exposures to dust have been reported. Fifteen of these cases revealed discrete nodular types of pulmonary lesions.

Differential diagnosis of solitary cavitary pulmonary lesions in the past has included tuberculoma, bronchogenic carcinoma, and lung abscess. With the report of the authors' case of a cavitary pulmonary rheumatoid nodule, this entity must now also be included.

The authors describe a patient with cavitary pulmonary rheumatoid nodule, also associated with chronic lipid effusion. The left pleural effusion contained, in addition to elevated lipids, very low glucose concentration and extremely high level of lactic acid dehydrogenase.

Of the 50 cases reported in the literature only 12 had characteristic pathologic findings similar to the subcutaneous rheumatoid nodules so commonly found in this entity.

The roentgenologic features of rheumatoid arthritis have been outlined in the past. Encysted pleural effusions have been found to be associated with the disease, but this has been ruled out in this particular case by lung biopsy. Association of pleural effusion and rheumatoid arthritis has been said to be more frequent in older individuals and there is an equal sex distribution.

Other tests considered to help, but which are not diagnostic, include low glucose level in the pleural fluid and high levels of lactic acid dehydrogenase, which incidentally is also found in the joint fluid. A high lipid content may also be found in 50 per cent of patients with tuberculosis.

The disease itself may be selflimiting and at present treatment is indeterminate, although steroids have been used.—*James R. Stevenson, Captain, MC*

Levin, Emanuel J., and Bryk, David. Dressler syndrome (postmyocardial infarction syndrome). *Radiology*, Oct., 1966, *87*, 731–736. (From: Department of Radiology, Maimonides Hospital, Brooklyn, N. Y.)

The essential elements of the Dressler syndrome (postmyocardial infarction syndrome) consist of pericarditis, pleuritis, and pneumonitis. These usually present in combination, but each may occur as a sole manifestation. The illness may be ushered in within a few days of the onset of the myocardial infarction or may be delayed as long as 8 weeks. Pain of the pleuropericardial type is typical, together with low-grade fever, leukocytosis, and elevation of the sedimentation rate. A persistent pericardial friction rub is found in about 80 per cent of the cases. The tendency toward relapse is a conspicuous feature of the syndrome, and there may be as many as 6 episodes, each lasting from 1 to 6 weeks. The prognosis is usually excellent, and the illness pursues a benign course. Steroid therapy usually will bring dramatic improvement even when the symptomatology is severe.

The roentgen findings consist of pericardial effusion, pleural effusion and pneumonitis. Pleural effusion and/or pneumonitis may exist alone or in combination but pericardial effusion is always associated with one or both of the others. Of the 52 cases upon which their report is based, 25 showed all three manifestations of this syndrome, and 22 showed pleural effusion and/or pneumonitis either alone or in combination but there were none with pericardial effusion unassociated with either pleural effusion or pneumonitis. Five cases had completely negative roentgen studies despite clinical evidence of the syndrome.

The differential diagnosis includes pulmonary embolization or infarction, another myocardial infarction, or extension of a previous myocardial infarction. None of these conditions, however, cause prolonged or relapsing episodes of fever, pericarditis, pleuritis, and pneumonitis. Roentgenograms which usually demonstrate a rapid increase in the size of the cardiac shadow and other features of pericardial effusion in association with pulmonary infiltrates and pleural effusion help in the differentiation of these other conditions. Attention is called to a characteristic widening of the superior mediastinum which is seen in about one-third of the cases.

The authors stress the importance of establishing the correct diagnosis because anticoagulant therapy, which is acceptable in the treatment of infarct, is contraindicated in the postmyocardial syndrome.—*Donald N. Dysart, M.D.*

Abdomen

Williams, J. L., and Wightman, J. A. K. Familial polyposis of the colon: report of a family with a 5-year follow-up of colectomy and ileorectal anastomosis. *Brit. J. Surg.*, Sept., 1966, *53*, 780–783. (From: Derbyshire Royal Infirmary, Derby, England.)

A previously unrecorded family with familial polyposis of the colon is reported with a 5 year fol-

low-up on 6 patients treated by total colectomy and ileorectal anastomosis.

Sigmoidoscopic examinations at 6 month intervals following operation have been performed with fulguration of any rectal polyps found. Over the 5 year period carcinoma has not occurred in the rectal stump. One patient with 2 carcinomata of the colon at the time of colectomy has no evidence of recurrence. One patient of 62 years refused colectomy and has developed carcinoma of the rectum with metastases to the regional lymph nodes.—*David Morse, M.D.*

Singh, Jasbir, and Boyd, Eldon M. The acute toxicity of tannic acid in the tannic acid-barium sulfate radiodiagnostic enema. *J. Canad. A. Radiologists*, Sept., 1966, *17*, 124–131. (From: Department of Pharmacology, Queen's University, Kingston, Ontario, Canada.)

The authors administered tannic acid as a retention enema to male albino rats in a volume of 20 ml./kg. In each instance the enema was retained for 4 hours utilizing an anal clamp and various concentrations of tannic acid.

Unexpectedly, the investigation disclosed that tannic acid is more toxic given by rectum than by mouth to albino rats. The lowest dose of tannic acid which produced minor signs of toxicity was 0.2 gm./kg. Death occurred at an average of 48 hours and the larger the dose the earlier the death. Important autopsy findings were extensive local inflammation with ulceration of colonic mucosa, hepatic necrosis and tubular nephritis.

The authors estimate from this study, that the maximal single nontoxic dose of tannic acid given as an enema is 0.1 gm./kg. or 1 liter of 0.5 per cent solution for adults.—*Francis P. Shea, M.D.*

Harrow, Benedict R., and Winslow, Oliver P. Renal toxicity following oral cholecystography with oragrafin (ipodate calcium). *Radiology*, Oct., 1966, *87*, 721–724. (From: Departments of Urology and Radiology, Baptist Hospital and the University of Miami, School of Medicine, Miami, Fla.)

The authors report a case of renal toxicity following oral cholecystography with oragrafin calcium (ipodate calcium). The patient, being investigated because of epigastric discomfort, had ingested 6 gm. of oragrafin on the night of admission to the hospital. The next morning roentgenographic studies revealed a densely filled normal gallbladder and the usual faint density of the kidneys. Following this, intravenous urography was performed with injection of 50 cc. of renovist (sodium and methylglucamine diatrizoate). Dense nephrograms occurred, beginning at 20 minutes and lasting at least 7 hours. No renal tract abnormality was found.

During the nephrographic phase, the patient experienced only some nausea and mild back pain. Blood pressure determination showed a transient elevation of both systolic and diastolic readings. At a follow-up study 3 months later, the patient was asymptomatic and a repeat intravenous urography with 50 cc. of renovist showed again a normal renal tract and no nephrographic effect was seen.

It is concluded that the dense nephrograms were due to a toxic effect of oragrafin which caused a sudden and precipitous decrease in renal blood flow due to constriction of the preglomerular blood vessels. The authors state that there is evidence that all the modern oral cholecystographic agents can produce this type of renal toxicity with acute tubular necrosis resulting in the more severe cases. Liver damage and double doses potentiate the renal toxicity. It is recommended that dosage schedules be carefully supervised in the agents showing a more pronounced and more rapid intestinal absorption.—*Donald N. Dysart, M.D.*

Christoforidis, A. John, and Nelson, Sidney, W. Radiological manifestations of ulcerogenic tumors of the pancreas: the Zollinger-Ellison syndrome. *J.A.M.A.*, Oct. 31, 1966, *198*, 511–516. (Address: Dr. Christoforidis, 410 W. 10th Avenue, Columbus, Ohio.)

The Zollinger-Ellison syndrome is characterized by gastric hypersecretion, hyperacidity, enteritis and atypical peptic ulceration associated with non-insulin producing islet-cell tumors of the pancreas.

Approximately 60 per cent of the ulcers discovered prior to the first operation occur in the duodenal bulb while 26 per cent are found in atypical locations. Gastric ulcer is found in 6 per cent. In 10 per cent multiple ulcers are present prior to the first operation.

Hypersecretion and hyperacidity occur in the majority of cases and are apparently due to stimulation of the parietal cells by a gastrin-like hormone elaborated by the ulcerogenic tumors. Approximately 60 per cent of these tumors are malignant and two-thirds have metastasized when first diagnosed. Occasionally diffuse hyperplasia of the pancreas is responsible and cure is impossible unless total pancreatectomy is performed.

Enteritis, clinically manifested by diarrhea, occurs in approximately 40 per cent of all cases. Its etiology is controversial.

In 14 cases personally reviewed by the authors the radiologic manifestations are described. In none of these cases was a primary esophageal ulcer demonstrated. However, following subtotal gastrectomy 3 patients developed a distal esophageal ulcer. Primary gastric ulcer was uncommon occurring in only 2

patients. More significant was the finding of markedly hypertrophied mucosal folds and large amounts of gastric fluid.

Nine patients presented with duodenal ulcer. Postbulbar ulcers should always raise the suspicion of the syndrome.

Peptic ulcers in the jejunum were found in 5 patients and when seen are almost pathognomonic of the Zollinger-Ellison syndrome.

The majority of patients did not have the correct diagnosis until after their fourth surgical procedure. Recurrent stomal ulcers following partial gastrectomy should suggest the diagnosis and lead to the correct surgical procedure, total gastrectomy.

In the group of patients who were correctly diagnosed and therefore initially treated by total gastrectomy a 100 per cent survival rate was achieved.—*Francis P. Shea, M.D.*

Giraud, M., Bret, P., Levrat, M., Croisille, M., and Bousquet, G. Exploration radiologique du pancréas par stratigraphie axiale transverse (bilan de dix années d'expérience). (Radiologic examination of the pancreas by means of transverse axial stratigraphy [summary of 10 years' experience].) *Ann. radiol.*, 1966, *9*, 563–578. (From: Service Central de Radiologie de l'Hôpital Edouard-Herriot, Lyon, France.)

In reporting on their 10 year experience the authors stress the value of transverse axial tomography in latent disease of the pancreas involving particularly the body and the tail. Disease of this area remains silent for a long time before it becomes clinically apparent. By the same token, routine radiologic studies of the biliary and gastrointestinal tract are usually not helpful.

In two-thirds of the cases examined the radiologic diagnosis of the gastrointestinal tract was normal. In cases of jaundice examination of the biliary tract was not possible and in the absence of jaundice, examination of the biliary tract was negative in the body-tail pancreatic lesions.

In a series of 62 cases of cancer of the pancreas and 130 cases of pancreatitis examined by transverse axial tomography, a positive diagnosis was made in one-third of each series.

The presence of calculi in the region of the pancreas is an indication of present or past disease of this organ. However, calculi may overlie the pancreas. They can be definitely localized, within or outside the pancreas, by means of transverse axial tomography.

While at times a differential diagnosis between enlarged pancreas due to pancreatitis and a large pancreas due to carcinoma cannot be made, the technique demonstrates the presence of an abnormal pancreas and definitely directs our attention to this area.

The examination is easily performed, causes no strain on the patient and can be readily carried out by a well trained and coordinated team of radiologist-technician.

Twenty-five figures representing reproductions of roentgenograms with explanatory diagrams accompany this excellent paper. These roentgenograms illustrate various types of pancreatic disease.—*William H. Shehadi, M.D.*

Genitourinary System

Hemley, Samuel D., Gallagher, Joseph, and Cusmano, Joseph. Large bolus injection with compression in routine excretory urography. *J. Urol.*, Sept., 1966, *96*, 390–393. (From: Department of Radiology, Englewood Hospital, Englewood, N. J.)

To improve the quality of intravenous pyelograms, the authors recommend a dosage referable to the body weight of the patient.

Conray 60 per cent was used in 255 cases and conray 66.8 per cent in 75 cases. The dosage recommended is 50 cc. for patients weighing 150 pounds or over, 42 cc. for patients of 125 to 149 pounds, 33 cc. for those of 100 to 124 pounds, and 25 cc. for patients weighing between 75 and 99 pounds.

Using a 19 gauge needle, the conray is injected intravenously as rapidly as possible, usually within 15 to 30 seconds. No previous testing for allergy is done. Films are exposed at the end of 3 minutes and 10 minutes with the patient in the supine position using compression over the pelvic ureters. The compression is then released and an additional film is exposed 1 minute later. At the end of 15 minutes a film is exposed with the patient in the prone position.

The most severe side reaction was pain in the arm experienced chiefly by those patients who received conray 400. Other side reactions consisted of nausea and vomiting and in a few cases urticaria, dizziness, sneezing and wheezing. Because of the arm pain, the authors do not recommend the use of conray 400 since its increased iodine content does not result in any increased density of the pyelogram.

In patients who have blood urea nitrogen above 25 mg. per cent, 50 cc. of contrast material is recommended.

The authors conclude that the use of a large bolus rapidly injected and with compression over the pelvic ureters significantly enhances the value of intravenous pyelography and does not subject the patient to any greater risk than in the customary routine procedure.

One table and one composite figure illustrate the results of this study.—*George W. Chamberlin, M.D*

Fournier, André-M. Urozonographie du nourrisson et du très jeune enfant (adaptation au polytome). (Urozonography in the newborn and infant [with use of the polytome].) *J. de*

radiol., d'électrol. et de méd. nucléaire, Oct., 1966, *47*, 507–520. (From: Service Central de Radiologie de l'Hôpital de la Conception, Marseille, France.)

The author uses the term *zonography* to denote the technique wherein small angles of the polytome (1° to 20°) are used. As sharp urograms in the newborn and infant require the elimination of superfluous gas shadows he has given up standard techniques in favor of the tomogram.

Nembutal is given 2 hours before the examination to induce somnolence. Linear movement is employed with the motion at right angles to the length of the patient. The gonads are protected with lead, except that they are uncovered in the last exposures in female patients. Contrast medium is injected intravenously when that is possible; if not, an increased dose mixed with hyaluronidase is given in each buttock while the patient is held prone.

The technical factors are: 50 to 65 kvp. according to the patient's size, 200 ma. and sweeps of 3–4°, which will give a thickness cut of 2 cm., or if gas shadows are excessive a sweep of 7° or more.

Zonograms are often spectacularly successful; the only inconvenience is the obtaining of proper settings to visualize the ureters.—*Frank A. Riebel, M.D.*

DeWeerd, James H., and Holman, Colin B. Television subtraction techniques in urography. *J. Urol.*, Oct., 1966, *96*, 578–582. (From: The Mayo Clinic and Mayo Foundation, Sections of Urology and Roentgenology, Rochester, Minn.)

The purpose of subtraction techniques in radiography is to eliminate undesirable and unnecessary shadows and to facilitate the interpretation of the significant shadows of the roentgenogram. The principle of the technique is to superimpose a negative and a positive film which have been exposed with the patient in the same position and on one of the films additional structures are radiographically demonstrated. This procedure is particularly applicable to arteriography wherein numerous structures, including the blood vessels themselves, are superimposed. The procedure is accomplished by exposing a film in the usual manner, and a second film in the same position after the injection of some opaque medium into the vascular system such as in renal arteriography or cerebral arteriography. A photographic positive is then made from the x-ray negative anteriogram. This is superimposed upon the original x-ray negative and studied in this manner or photographed for future reference.

The authors have improved upon this technique by using closed circuit television technique which eliminates the tedious exacting photographic manipulations which are necessary for the standard techniques. Two television cameras with a single synchronized circuit are mounted to scan 2 roentgenograms and apply their images simultaneously through a single monitor. The output signal of one camera is reversed so that the roentgenogram being scanned is converted to a positive image. Controls are provided for the image in one camera to be electrically enlarged or contracted or moved horizontally or vertically in order to supply as nearly a perfect matching of the two images as possible. The contrast and density of the television monitor screen can be changed within limits to enhance the diagnostic qualities of the picture. Magnification by this method is possible by changing the lenses of the television camera. The subtracted image visualized on the monitor screen is photographed with Polaroid film. While this technique may be applied in retrograde urography, it is most applicable to the study of blood vessels after opaque media injection.

The authors illustrate the principle with subtraction technique films taken from a television monitor and showing retrograde pyelograms, renal arteriograms, pelvic arteriograms in bladder lesions, and nephrotomograms. Unfortunately, the detail in these illustrations is partially lacking because of inherent limitations of the technique.—*George W. Chamberlin, M.D.*

Hodson, C. J., and Craven, J. D. The radiology of obstructive atrophy of the kidney. *Clin. Radiol.*, Oct., 1966, *17*, 305–320. (From: University College Hospital, London, W.C.1, England.)

The changes produced by extrarenal urinary obstructive, or "back pressure," atrophy of the kidney have been studied by the authors. Fifty consecutive patients were investigated. In 34 of these there was evidence of present or past urinary tract obstruction. In the remaining 16 patients renal changes were found which were probably due to temporary urinary tract obstruction, such as by a stone, with either indefinite or no notable symptoms.

The diagnostic features of obstructive, or "back pressure," atrophy are: (1) (*a*) a loss of substance of the renal papillae, generalized and uniform throughout the whole kidney, (*b*) an appearance of "pairing" of the renal calyces due to an increased distance between them across the sagittal plane of the kidney, and a partial rotation of the kidney about its vertical axis; (2) a decrease in renal substance thickness, equal throughout the kidney, in addition to decrease in size of papillae; (3) dilatation, variable in degree, of the renal pelvis and calyces; (4) a difference in size of the kidney as compared with the opposite side, the affected kidney being either larger or smaller than the other; and (5) a reduction in the rate of urine production.

In differential diagnosis one must consider chronic pyelonephritis, papillary necrosis, and renal tuberculosis. Chronic pyelonephritic scarring is essentially

irregular in distribution and degree throughout the kidney. The outline of the kidney is usually uneven. One or more papillae may be normally recognizable, while the others have undergone necrosis, with clubbing of the calyces. Both the ulcerative and cicatricial forms of renal tuberculosis produce individual clubbing of the calyces, but never of an even, generalized distribution. Papillary necrosis with calycine clubbing occurring in diabetes and with prolonged intake of phenacetin is generally quite uneven, and it resembles pyelonephritic scarring more than obstructive atrophy.

The types of renal change resulting from urinary obstruction may be classified as follows:

(1) Obstructed kidneys
  (a) enlarged obstructed kidneys
  (b) diminished obstructed kidneys
(2) Postobstructive kidneys
  (a) enlarged, with papillary atrophy
  (b) diminished, with papillary atrophy
  (c) diminished, without or with minimal papillary atrophy

The authors conclude that radiology probably offers the only reliable means of defining during life the changes of obstructive atrophy. By the time the patient comes to autopsy the picture may be complicated by arteriolar sclerosis, hypertension, superimposed infection, or previous surgery.—*Samuel G. Henderson, M.D.*

Palumbo, Betti R., De Santis, M., Senin, U., and Biasini, E. Use of mercury-203 scintiscan in experimental renal trauma. *J. Urol.*, Sept., 1966, *96*, 278–282. (From: Departments of Internal Medicine and Surgery, University of Perugia School of Medicine, Perugia, Italy.)

The authors discuss the limitations of urography and pyelography in the estimation of the presence and degree of renal trauma and then offer evidence to support their opinion that scintiscanning may be a more helpful procedure for this purpose. Twelve anesthetized dogs subjected to unilateral renal trauma were injected with chlormerodrin Hg^{203} (2.5 mc/kg.) 10 to 60 minutes after the trauma, and scannings were made 20 to 60 minutes following the isotope administration. In some cases, the scanning was repeated in 2 to 3 hours. Excretory urography was also obtained in most cases and in several retrograde pyelography was performed.

The authors used Patel's classification of renal trauma into 4 groups: (1) hemorrhagic infiltration by contusion, whereby the renal capsule and calyces were not damaged; (2) laceration of the renal capsule and parenchyma openings into one calyx; (3) renal fracture with laceration of the capsule and the excretory tract; and (4) fragmentation of the kidney.

Scan interpretation included estimation of difference in degree of shading of the kidneys and the appearance of the margins of each renal shadow.

Normal scans were the rule in Group 1. Group 2 showed moderate decrease in shading contrast and moderate irregularity in profile of the traumatized kidney. Group 3 showed more marked decrease in contrast and alteration in outline, and Group 4 showed complete destruction of organ profile and very poor fixation of the isotope in the renal parenchyma.

The changes are apparently the result of tubular damage and not decreased renal blood flow due to hypotension.

The findings indicate that scintigraphy is a valuable aid in determining the localization and extent of the traumatic lesion.—*George W. Chamberlin, M.D.*

Dinkel, L. Nephrocalcinosis and dichystrol (dihydrotachysterol) medication. *German Med. Monthly*, Sept., 1966, *11*, 357–360. (From: Private Radiological Institute Dr. L. Dinkel, Heilbronn, Germany.)

Successful postoperative treatment of tetany by means of pure vitamin D_3, which has the advantages of a more predictable and prolonged effect than parathormone, has gradually led to the widespread acceptance of vitamin D_3 in the management of various forms of tetany.

The author reports a case of a 32 year old woman with extensive bilateral nephrocalcinosis affecting predominantly the renal medulla after longterm dichystrol therapy. Fine vascular calcification, circumscribed cystic changes in the head of the fibula and moderate hyperostosis frontalis interna were additional features.

He concludes that at the present time, long term maintenance on dichystrol and the possible effects of overdosage can no longer be regarded as fundamentally harmless. Regular estimations of serum calcium level are considered essential, especially in the so-called normocalcemic form of tetany, and attention is called to the ever present dangers of renal insufficiency.—*C. Peter Truog, M.D.*

Wagman, Edward, Barbara, Anthony, Marquis, James, Chirls, Marvin, and Falla, Anita. Renal fat embolization and urostealith formation complicating femoral fracture. *J.A.M.A.*, Nov. 14, 1966, *198*, 721–723. (Address: Dr. Wagman, Bergen Pines Hospital Laboratories, Paramus, N. J.)

Lipuria occurring with femoral fractures in 3 female Negro children, and persisting for 1–5 months is the basis for this report.

In one case, fatty "calculi" and renal colic with hematuria were observed. Urostealiths were passed spontaneously after intravenous pyelography and

were found to consist of fat globules and fatty acid crystals.

All cases became asymptomatic and none had loss of renal function.

Lipid studies on these patients and their families eliminated idiopathic hyperlipemia as a factor.—*Richard E. Kinzer, M.D.*

HUMPHRY, A., and MUNN, J. D. Abnormalities of the urinary tract in association with congenital cardiovascular disease. *Canad. M. A. J.*, July 23, 1966, *95*, 143–145. (From: Department of Radiology, Hospital for Sick Children, Toronto, Ontario, Canada.)

In order to determine the types and incidence of urogenital abnormalities in patients undergoing angiocardiographic procedures, the authors secured an abdominal roentgenogram on each of 400 such patients. All were children. Sodium diatrizoate 75 per cent was used in amounts varying from 10 to 40 cc., and the abdominal roentgenogram was taken 20 to 30 minutes following the injection.

Over-all urinary tract abnormality was found in 5.5 per cent (24) of the group. The disease was serious in 2 per cent (9 children). The abnormal findings in 15 of the 24 consisted of bifid collecting system, horseshoe kidney, rotated kidney, and ectopic kidney. The more serious diseases included ureterocele, renal agenesis, severe hydronephrosis, stenosis of the urethra, atresia of the ureter, and cystic kidney.

Comparison of the urograms of this group with urograms of another 400 pediatric patients revealed no significant difference between the two groups in the incidence of renal anomalies. Nor could a specific association be found between the various urogenital and cardiac malformations.

The authors conclude that the securing of an abdominal roentgenogram following angiographic procedures clearly has value; namely, finding unsuspected, serious genitourinary abnormality.—*Justin J. Wolfson, M.D.*

PRITZL, DONALD J., and BORS, ERNEST. Is cystourethrography of neuro-urologic diagnostic value in patients with spinal cord injury? *J. Urol.*, Sept., 1966, *96*, 320–327. (From: Spinal Cord Injury Service and the Urology Section of the Surgical Service, Veterans Administration Hospital, Long Beach and the Department of Surgery, University of California, School of Medicine, Los Angeles, Calif.)

This study is an attempt to correlate the location of the lesion in the spinal cord or cauda equina in relation to the radiographic appearance of the cystourethrogram. It is also an attempt to evaluate the catheter status and time lapse after the spinal cord injury on the cystourethrogram.

One hundred and twenty-five patients were evaluated clinically and roentgenographically with a minimum follow-up of 6 years after spinal injury; 496 roentgenograms were reviewed and any patients who had upper urinary tract diversion procedures were eliminated from the study. Eighty-eight patients had upper motor neuron lesions and 22 had lower motor neuron lesions. Evaluations of the bladder were made according to its degree of contraction, trabeculation, or normalcy. The bladder neck was considered dilated if it measured 1.5 cm. or more. The urethra was considered patulous when its various components could not be easily identified because of dilatation.

Only 11 of 125 patients had stable cystourethrographic findings during their entire post-traumatic follow-up. These 11 probably reflect the individual patient's ability to cope with urinary tract infection and better bladder hygiene. There was no apparent correlation between bladder stability and catheter status or level and extent of the injury in the spine.

A patulous urethra associated with a tendency to a contracted bladder was observed in 24 of 125 patients. A slightly higher percentage of these people had upper motor neuron lesions than lower motor neuron lesions. There was no apparent correlation between the patulous urethra, the catheter status level, and the extent of the spinal cord lesions. Fourteen of the 24 patients with patulous urethras subsequently demonstrated a reversal to competent urethral configuration. This is associated with many variables such as technique and infection.

Of 125 patients, 114 demonstrated progressive, often times variable and frequently intermittent, cystourethrographic findings during their follow-up period of 6 to 16 years. The authors conclude that the cystourethrographic appearance alone is not of neuro-urologic diagnostic value. It is incorrect to believe that the appearance of a cystourethrogram is pathognomonic for the extent or level of the spinal cord lesion. Catheter status and time lapse do have a definite bearing on the appearance of the cystourethrogram in patients with spinal cord lesions. The heaviest degree of bladder trabeculation which is described as a "Christmas Tree" bladder was not of diagnostic value for the level or type of spinal cord lesion. This occurred more frequently in patients without catheter drainage than those with catheter drainage and it was somewhat more frequent in patients with lower motor neuron lesions than those with upper motor neuron lesions.—*George W. Chamberlin, M.D.*

SKELETAL SYSTEM

HARRISON, M. H. M., and MENON, M. P. A. Legg-Calvé-Perthes disease. *J. Bone & Joint Surg.*, Oct., 1966, *48-A*, 1301–1318. (From:

Royal Orthopaedic Hospital, Birmingham, England, and Medical College Hospital, Trivandrum 11, Kerala, India.)

In the past 50 years since Legg, Calvé, Perthes, and Waldenström described osteochondritis of the upper femoral epiphysis, a number of methods of clinical management have evolved. Since material for laboratory examination is rarely available, an objective index for the evaluation of clinical methods would be desirable.

The technique for measurement of the femoral head as described by Heyman and Herndon was used (1) in an attempt to graphically record the progress throughout the course of the disease and (2) to compare the effectiveness of various treatments in 74 matched patients.

The method consists of 4 separate quotients obtained by measuring various parameters of both the affected and normal hips directly from the roentgenogram. Each quotient reflects a feature of the hip anatomy and a fifth or comprehensive quotient which is the mean of the other 4 quotients and is a numerical expression of the over-all shape of the hip. The higher the quotient the more closely the diseased hip approaches normal parameters.

This method, however, is not usable in bilateral disease and has about 5 per cent error estimated in each quotient. The method is more reliable if all the measurements are made by a single observer. Furthermore, only the shape of the femoral head is evaluated and not the texture or density.

Four effects of treatment were noted as follows: (1) improvement with reversal of deformity; (2) decrease in rate of deformation but progress of disease not halted; (3) no effect on the course of the disease; (4) adverse effect of treatment with improvement after treatment is discontinued. The graphs appear to succeed in following this progress.

In comparison of treatment methods, the treatment with non-weight bearing abduction casts demonstrated superiority over other methods such as Pugh traction and hip spica immobilization.

Theoretic considerations of femoral head containment by this method and its technique are discussed by the authors.

The main objective of the study is to challenge therapeutic complacency and advocate objective assessment of management.—*Edward R. Savolaine, Captain, MC*

Molloy, Maureen K., and MacMahon, Brian. Incidence of Legg-Perthes' disease (osteochondritis deformans). *New England J. Med.*, Nov. 3, 1966, *275*, 988–990. (From: Department of Epidemiology, Harvard School of Public Health, Boston, Mass.)

From reports of orthopedists, hospitals and the State Crippled Children's Service 87 cases of Legg-Perthes' disease were identified as being newly diagnosed in 1964 in Massachusetts residents. Eighty-six of these cases were in white residents, while 1 case was a Negro resident. Seven of the 87 cases were bilateral at the time of first diagnosis. These 7 were all males.

Among the unilateral cases, in 58 per cent (46 cases) the left hip was affected. This figure does not differ significantly from a theoretic expectation of 50 per cent. Most of the cases occurred between the ages of 3 and 8 years. The disease is 5 times as frequent in boys as in girls. Estimates of the cumulative incidence to 15 years of age ("attack") were 1:740 males and 1:3,700 females.

The authors state that Legg-Perthes' disease is usually considered an uncommon, if not rare, condition. Their estimates suggest that the disease is by no means uncommon and is one that should be well represented in general pediatric experience.—*C. Peter Truog, M.D.*

James, Wilson, and Moule, Brian. Hypophosphatasia. *Clin. Radiol.*, Oct., 1966, *17*, 368–376. (From: The Southern General Hospital, Glasgow, Scotland.)

Hypophosphatasia is a condition characterized by skeletal changes resembling severe rickets histologically and by low serum and tissue alkaline phosphatase. The authors describe 5 cases, 3 of these being recognizable in the neonatal period, the 4th and 5th cases developing symptoms characteristic of the condition after several months following birth.

From the clinical standpoint the earlier the age at presentation the more severe are the presenting features. The newborn cases tend to be severely affected. A second group comprises less severely affected infants and childhood cases, and a third group consists of the few cases seen in adult life. In severely affected infants it is evident that the pathologic changes were present *in utero*. Common symptoms are failure to thrive, vomiting, irritability, jerky movements, convulsions and intermittent pyrexia without evidence of infection. In less severely affected infants this clinical picture is later in onset and the prognosis is better. The skull in the first group is balloon-like, less so in the second group. There is wide separation of the cranial "sutures," with a wide, bulging anterior fontanelle. A rickety rosary and swelling at the wrists and ankles are commonly seen. There is a marked tendency toward craniostenosis as the child becomes older. In cases with later onset there are delayed onset of walking, poor gait, genu valgum, pains in the arms and legs, short stature, and dental abnormalities, such as caries and premature shedding of deciduous teeth.

Radiologically the long bones show the most obvious changes. There is grossly irregular ossification of the metaphysis, giving a "frayed" or "tufted" appearance. In rickets the decalcification tends to be

regular, giving a "ground glass" appearance to the affected metaphysis. Marginal metaphyseal infractions are common. The epiphyses are small and appear late in severe cases. Here, too, there is irregular calcification with an abnormal trabecular architecture. In the skull there are large areas of uncalcified osteoid in the membranous bones in the regions adjoining the "sutures" and to a lesser extent at the base. Premature loss of the teeth seen in hypophosphatasia is otherwise a rare condition in children.

The differential diagnosis includes: (1) rickets and osteomalacia; and (2) osseous dystrophies. In hypophosphatasia the diagnostic triad consists of clinical and radiologic changes resembling severe rickets, a low serum alkaline phosphatase level and phospho-ethanolamine in the urine.—*Samuel G. Henderson, M.D.*

Bonucci, E., and Agostinelli, O. Radiological and microradiographic features in a case of congenital hypophosphatasia. *Radiol. clin. et biol.*, 1966, *35*, 80–92. (Address: Istituto di Anatomia Patologica dell'Università di Pisa, Pisa, Italy.)

Congenital hypophosphatasia is a chronic hereditary disease characterized by defective ossification and abnormally low alkaline phosphatase activity in serum and tissues. The authors report the case of a 45 day old male infant whose alkaline phosphatase activity in the serum ranged between 1 and 5 King-Armstrong units. The mother and 2 sisters had abnormally low enzymatic activity. Both parents, who are cousins, had small amounts of phospho-ethanolamine in urine examinations.

The authors discuss the roentgenologic findings in detail. Specifically, the bones of the skull showed poor mineralization which was particularly evident in the perimeter of the parietal bones. The intracranial sutures were very large. The long bones of the arms and legs had a rather uniform morphology, all being abnormally short and characterized by grossly distorted metaphyseal regions. Distortion was most striking in the humeri which had jagged edges. In addition the metaphyseal texture was rarefied and the bone trabeculae were thin and discontinuous. The provisional zone of calcification was difficult to identify. The ossification centers of the epiphyses were small, irregularly shaped, often uncalcified and separated from the metaphyseal portions by a very wide physeal zone. Metaphyseal infraction was noted through the distal end of the left radius and left ulna with abduction of the wrist. The characteristics of the disease were similar in other bones, particularly the ribs, vertebral bodies and bony pelvis.

The patient died at the age of 70 days with symptoms of cardiac and pulmonary failure. Although a complete postmortem examination was not performed, the left femur was made available. Microradiography confirmed the *in vivo* roentgenographic appearance; hematoxylin and eosin stained sections demonstrated that the trabeculae in the metaphyseal zone were irregular and randomly ordered, consisting of organic matrix alone.

Congenital hypophosphatasia seems to be an inherited metabolic defect with a recessive mode of transmission. The major result of alkaline phosphatase deficiency is that osteoid and cartilaginous matrix fail to mineralize. This is reflected in the roentgenographic appearance because the provisional calcification lines are missing. The jagged and areolar metaphyseal lines observed are due to cartilaginous cells failing to disintegrate and hence due to the persistence of tongue-like cartilaginous processes between newly formed trabeculae. The porotic diaphyseal areas are the result of large zones of osteoid matrix and the fractures of the metaphysis are due to its softness. In like fashion, the enlarged cranial sutures and the disproportionately large amount of translucent tissue around the vertebral bodies are the result of the failure of organic bone matrix to mineralize.

As regards the differential diagnosis, the major entity to be excluded is florid rickets caused by vitamin D deficiency. The differentiation can be made without difficulty clinically and the changes are usually less marked roentgenographically.—*Lionel W. Young, M.D.*

Dalla Palma, L., and Cavina, C. Turner's syndrome: radiological appearances. *Radiol. clin. et biol.*, 1966, *35*, 65–79. (Address: Istituto di Radiologia dell'Università, Firenze, Italy.)

The authors indicate that the term "gonadal dysgenesis" in subjects with female phenotype refers to an abnormal development of the gonads, which can be completely lacking, rudimentary or hypoplastic. They consider gonadal dysgenesis in two forms, namely the Turner's syndrome (classical or mild) and simple gonadal dysgenesis. In distinguishing Turner's syndrome from simple gonadal dysgenesis, patients with the former have a short stature while those with the latter may have a short, normal or tall stature of eunuchoid type. Moreover, the nuclear chromatin is nearly always negative in Turner's syndrome and it is nearly always positive in simple gonadal dysgenesis.

The authors report on 46 patients who have had various roentgenologic examinations. They indicate that pneumopelvigraphy may sometimes show a small ovoid opacity on either side which to them represents a hypoplastic ovary.

The skeletal changes and in particular those seen in the knees and hands are emphasized. These are: (1) enlargement of the epiphysis which extends medially and downward; (2) flattening of the articu-

lar medial cortex, which is also sometimes depressed; (3) deformation of the border between the metaphysis and the diaphysis, which is sometimes sharply curved or sometimes angled; and (4) in a few cases the presence of a beak-like exostosis which projects medially under the condyle.

Although the authors state that most patients examined showed fourth metacarpal shortening, they do not indicate its incidence for either hand or foot. Neither is the incidence of the cardiovascular malformations given.—*Lionel W. Young, M.D.*

Malka, S. Idiopathic aseptic necrosis of the head of the femur in adults. *Surg., Gynec. & Obst.*, Nov., 1966, *123*, 1057–1065. (From: University Department of Orthopedics and Traumatology, State Hospital of Geneva, Geneva, Switzerland.)

Aseptic necrosis of the femoral head accounts for 2–3 per cent of all chronic degenerative lesions of the hip. It favors males 4:1 and occurs primarily in adolescence and middle age. The hips are affected equally, and in 40 per cent bilaterally but rarely simultaneously.

The author reports 6 cases, 5 of which had bilateral involvement.

Clinically, the disease develops in 3 stages. (1) The stage of onset consists of abrupt, knife-like pain in the inguinal or gluteal region which radiates to the thigh and knee with no physical or roentgenographic findings. (2) The stage of roentgenologic findings occurs 2–6 months later and consists of discontinuity in the circumference of the femoral head and zones of irregular condensation, usually triangular in shape, in the femoral head. Decreased limitation of motion, particularly internal and external rotation and to a lesser extent abduction and adduction are present. (3) The stage of complication occurs at variable times and consists of lesions similar to osteochondritis dissecans, followed by flattening of the femoral head and incongruence of the articular surfaces.

Pathologically, there are 3 separate zones: the zone of necrosis, which is wedge-shaped with the apex towards the center of the bone; this is surrounded by a zone of fibrosis; the last zone is one of viable sclerotic bone.

There are two main groups of idiopathic aseptic necrosis of the femoral head. (1) One group includes those cases in which no provocative conditions existed and only hereditary and constitutional factors are considered to be influential. In men, alcoholism occurs in a significant percentage and in women estrogen insufficiency appears to be a factor. This latter effect may be due to the vasoconstriction and osteoporosis found in the postmenopausal period. (2) The second group consists of patients with aseptic necrosis of the femoral head as a complication of such conditions as hyperuricemia, corticotherapy, Gaucher's disease, sickle cell anemia, and congenital malformations and dysplasias of the hip.—*James R. Stevenson, Captain, MC*

Blickenstaff, Loren D., and Morris, James M. Fatigue fracture of the femoral neck. *J. Bone & Joint Surg.*, Sept., 1966, *48-A*, 1031–1047. (From: U. S. Army Hospital, Fort Ord Infantry Training Center, Fort Ord, California, and the Department of Orthopaedic Surgery, University of California School of Medicine, San Francisco, Calif.)

The authors point out that until recently this has been considered a relatively rare condition. However, they have encountered 41 fatigue fractures of the femoral neck in 36 patients. All occurred in men undergoing the first 8 weeks of basic infantry training after induction into the United States Armed Forces. The average age of these patients was 22½ years.

They divide these fractures into 3 main groups.

In Type 1 there were fractures with endosteal callus, periosteal callus or both, without a visible fracture line. Initial roentgenograms of 9 of these patients was considered normal and in 2 cases subsequent roentgenograms remained normal in appearance for 2 weeks before sclerosis was seen. All were treated by conservative means and recovered uneventfully.

In Type 2 fracture lines were present in the calcar region or across the neck but there was no displacement of the fragments. One-quarter of this group had fatigue fractures in other bones of the lower extremities but none had bilateral fractures of the femoral necks. Initially it was believed that these fractures should be treated conservatively without open reduction but the authors are now of the opinion that once a complete fracture line or significant calcar crack is seen early internal fixation should be employed.

In Type 3 displaced fractures were present. Nine patients fell into this category. Roentgenograms made on admission showed displaced fractures in 8 of these patients but 1 had a normal appearing roentgenogram made 4 days earlier. In the ninth patient the fracture line was seen 4 days after admission to hospital and the displacement occurred while he was in bed. Internal fixation was employed in this group and complications consisting of malunion, nonunion and avascular necrosis were common. This course of events is attributed to poor reduction and to the nature of the fracture which occurs in osteoporotic bone.

The term fatigue fracture may be misleading in that frequently no overt fracture line is seen. Fatigue (or stress) fracture is actually a process, an alteration of bone resulting from stress. A fracture may or may not develop and if it does it can be considered as a complication of the stress reaction.

Although this entire series is confined to military

subjects, the authors feel that the overweight white collar worker who goes on a strenuous fishing or hunting trip or starts on a program of vigorous exercise, or the teenage athlete who pushes himself to the maximum at the start of the season may well incur a fatigue fracture. If the physician is not sufficiently aware of the possibility of such a fatigue fracture and serial roentgenograms are not made, such a fracture remains undiagnosed.—*Arthur E. Childe, M.D.*

COVENTRY, MARK B., HARRISON, EDGAR G., JR., and MARTIN, JACK F. Benign synovial tumors of the knee: a diagnostic problem. *J. Bone & Joint Surg.*, Oct., 1966, *48-A*, 1350–1358. (From: Section of Orthopedic Surgery and of Surgical Pathology, Mayo Clinic and Mayo Foundation and the Mayo Graduate School of Medicine, University of Minnesota, Rochester, Minn.)

Benign tumors of the synovium, although infrequently encountered, may present a problem in the differential diagnosis of knee joint dysfunction. The authors have summarized the data on 55 cases from the files of the Mayo Clinic for the years 1945 through 1954 as follows.

Osteochondromatosis. Twenty-seven patients between the ages of 14 and 65 years demonstrated this condition. While usually typical in radiographic appearance, it must occasionally be distinguished from osteochondritis dissecans, trauma, or degenerative disease. This multicentric lesion is treated with synovectomy but tends to recur.

Pigmented villonodular synovitis. Twenty-seven cases were encountered ranging in age from 22 to 63 years. This synovial disease is usually encountered in the lower extremity and consists of villous proliferations of the synovial membrane and infiltration by hemosiderin laden stromal cells. The roentgenogram may show juxta-articular cystic changes or may be normal. Synovectomy is the treatment of choice.

Xanthoma. Nineteen cases of xanthoma were recorded ranging in age from 20 to 70 years. These solitary, circumscribed lesions are related histogenetically to pigmented villonodular synovitis but have less of a hemosiderin and lymphocytic component. Local resection without synovectomy is indicated.

Hemangioma. Eleven cases of this condition were recorded and were noted to fall within the adolescent and young adult age group. A long history of knee disturbance prior to diagnosis is usual. Atrophy of the thigh and cutaneous hemangiomas are a common association. Wide and thorough excision is required for cure.

Lipoma. Eight patients had lipomata found at arthrotomy. While common in the extremities, lipomata do not occur often in the synovial tissue. The lesions may be arborescent with multiple extensions so that complete removal is necessary for relief.

Preoperative localization of the small synovial tumor is important in that they may be obscure and difficult to find at arthrotomy.—*Edward R. Savolaine, Captain, MC*

LINSCHEID, RONALD L., and DAHLIN, DAVID C. Unusual lesions of the patella. *J. Bone & Joint Surg.*, Oct., 1966, *48-A*, 1359–1366. (From: Mayo Clinic and Mayo Foundation, Section of Orthopedic Surgery and of Surgical Pathology, Rochester, Minn.)

While the patella is commonly involved in traumatic and degenerative processes, and less commonly involved in systemic disease such as Paget's disease or hematogenous osteomyelitis, occurrence of neoplastic or neoplasm simulating disease is quite rare.

A review of the files of the Mayo Clinic for such lesions of patella revealed only 7 cases in this category, all of which were benign conditions but 1.

Case reports of the above lesions are included by the authors and represent 1 of each of the following: benign osteoblastoma, aneurysmal bone cyst, hemangioma, chondroma, lesion of hyperparathyroidism, an unclassified benign giant cell variant, and a metastatic lesion of malignant lymphoma. The proximal pole of the patella was most commonly involved.

These patellar lesions had in common a well circumscribed lytic appearance and also produced similar symptoms, which were largely the result of the mechanical forces exerted against the patella. Exaggeration of symptoms was noted with direct pressure on the patella or indirectly by flexion of the knee.

Although more than 29 cases of benign giant cell tumor of the patella have been reported in the literature, most of these tumors probably represent various benign giant cell containing entities that are now recognized. No genuine case of giant cell tumor of the patella has been recognized in more than 150 giant cell tumors of bone in the files of this clinic.

Primary malignant tumors of the patella are exceedingly rare. None of the more than 1,260 primary malignant bone tumors in the Mayo Clinic files has arisen in the patella.

Small cystic lesions of the patella may be overlooked or be ascribed to more common conditions. Their importance is, however, that they respond well to simple surgical management.—*Edward R. Savolaine, Captain, MC*

WILSON, D. W. Functional capacity following fractures of the os calcis. *Canad. M. A. J.*, Oct. 29, 1966, *95*, 908–911. (Address: Clinical Research Fellow, Accident Service, Royal Victoria Hospital, Montreal, Quebec, Canada.)

The author reviewed the results of 49 fractures of the os calcis in 45 patients from the Accident Service of the Royal Victoria Hospital, Montreal. By age

distribution 29 of the 45 patients were in the 20 to 50 year group, which is usually the principal wage earning period. It is for this reason that good results of healing and return of function are paramount.

The fractures were classified according to Watson-Jones, and fell into the following distribution: Type I-18; Type II-3; Type III-4; Type IV-7; and Type V-17. Types I, II, and III were all treated by conservative means with ace bandage or plaster cast as needed. One patient in Type II and 3 patients in Type IV needed closed manipulation. In the Type IV and V fractures, manipulation and arthrodesis were used.

In 3 of the 49 fractures, pseudo-arthrosis developed and 1 patient had incomplete healing due to infection, at follow-up. The rest all had satisfactory healing roentgenographically. Various parameters of function were used which generally showed quite satisfactory results. It is noted that with Type IV and V injuries the restrictions to function were somewhat greater. Of especial interest is the fact that in the Type IV and V injuries which were treated with immediate rather than delayed subtalar fusion, the results were better and the patients returned to work earlier.

Twelve of the 45 patients had to change occupations, but were still able to work; the remainder resumed their usual occupation. The time varied from 3 months off work to 1 year with 2 exceptions: 1 patient was off for 2 years and 3 months, and 1 for 4 years.—*George A. Kling, Captain, MC*

Ford, Lee T., and Goodman, Floyd G. (St. Louis, Mo.). X-ray studies of the lumbosacral spine. *South. M. J.*, Oct., 1966, *59*, 1123–1128.

The authors recommend the use of roentgenographic studies in several positions to aid in the evaluation of disturbances in the lumbosacral spine. They have added roentgenograms made in the standing position and lateral views in flexion and extension to their diagnostic armamentarium. They review the office roentgenographic findings in 1,614 patients, presenting with complaints referred to the low back with or without sciatica. Furthermore, they point out the aid of lateral roentgenograms of the lumbosacral spine taken in flexion and extension (stress positions), and the advantage of taking certain of these roentgenograms in the standing position.

The 1,614 sets of films were reviewed, interpreted, and the abnormal findings recorded and tabulated.

In the series, there were 945 males from 8 to 73 years of age, averaging 43.3 years of age; there were 669 females aged 11 to 83, averaging 41.5 years of age.

The findings were as follows: lumbarization of the first sacral vertebra was noted in 6 patients, while sacralization of the last lumbar vertebra occurred in 129 cases. This was bilateral in 62 cases and unilateral in 69 cases.

Asymmetry of facets was present in 181 of the patients, but was most common (107 patients) at the lumbosacral level.

Degenerative changes were present in 764 patients (47.5 per cent). Eight hundred and eighty-six patients (55 per cent) showed narrowing of one or more disk spaces in the lumbar spine.

Abnormal vertebral instability, demonstrated by the lateral extension and flexion roentgenograms was demonstrated in 336 (22.6 per cent) of the patients and always occurred at the lower 3 interspaces.

True spondylolisthesis with bilateral defects in the pars interarticularis or isthmus of the vertebra was present in 117 patients (7.2 per cent). The spondylolisthesis was located in the lumbosacral area in 95 patients, and spondylolysis occurred in 170 or 10.5 per cent of the patients presenting with low back pain symptoms. The pars interarticularis defects were bilateral in 121 cases and unilateral in 49 patients.

Other abnormalities were:

*"Ballooning" of the disk—number of disks involved	38
Calcification of the disk space	4
*Charcot spine	1
Destructive processes—osteoblastic or osteolytic	15
*Epiphysitis recent and remote—number of vertebrae involved	13
Fractures or fracture deformities of the vertebrae—number of vertebrae involved	59
*Fractures of the facet or presence of an extra ossicle—number of facets involved	4
Kissing spines	16
*Osteoporosis	81
*Osteomyelitis or infection of the disk space	9
Schmorl's nodes—number of vertebrae involved (frequently more than 1 vertebra involved per patient)	150
Scoliosis or list (17.5 per cent)	283
Spina bifida occulta	285
Synostosis (congenital)	3

The authors conclude with the hope that more examiners will use these additional aids in plain roentgenographic studies of patients with low back pain with or without sciatic pain.—*C. Peter Truog, M.D.*

* *Figures derived from last 1,047 patients.*

Owen, L. B., Eskey, C. W., Kashatus, W. C., and Brady, L. W. Multiosseous osteosarcoma: report of one case and review of the literature. *Radiol. clin. et biol.*, 1966, *35*, 43–60. (From: Departments of Radiology, Orthopedics and Pathology, Hahnemann Medical College, Philadelphia, Pa.)

An unusual case of osteosarcoma with involvement of both distal femora at the time of diagnosis and

subsequent multiple bone lesions prior to the development of pulmonary metastatic disease 6 months later is reported.

The English language literature encompassing 16 well documented cases of osteosarcoma with multiple bone lesions is reviewed. Of these cases, 8 presented with more than one bone lesion and no evidence of lung metastases.

Various theories of multicentricity of origin are presented.

In favor of multicentricity of origin is the fact that bone metastases are unusual in osteogenic sarcoma and that the multiple lesions occurred in a favorite site for primary osteogenic sarcoma. The absence of pulmonary metastases is against hematogenous spread from a single focus and lends further argument in favor of multicentricity of origin. The authors recognize that there are no known methods of either proving or disproving a multicentric origin of a femur.

On the other hand, lesions have been reported in bones which are rarely the site of primary osteosarcoma, *e.g.* carpal and tarsal bones. Also, in most of the cases reported, although no pulmonary metastases could be found, they present at autopsy and it can be reasonably concluded that they were present microscopically when the patient was alive. Some doubt is cast on this idea by the fact that it took several months for pulmonary metastases to be seen in multiple areas of bone metastases.

Batson's vertebral vein system provides a better explanation of distant osseous metastases in the absence of pulmonary lesions, particularly when there is a substantial period of time ensuing after detection of bone lesions and before pulmonary metastases appear.

In the absence of good evidence to substantiate retrograde flow of blood in the valveless veins of the extremities in continuity with the vertebral system, it is difficult to explain as metastatic lesions in both distal femora in a patient with no pulmonary metastases.

The prognosis in multiple osteosarcomas does not appear to be significantly different from that of a solitary osteosarcoma.—*Lawrence H. Gold, M.D.*

Blood and Lymph System

WHITE, J. J., SKINNER, G. B., and MACLEAN, L. D. Hepatoportography via the umbilical vein: a superior approach to diagnosis in liver disease. *Canad. M. A. J.*, Nov. 12, 1966, *95*, 997–1003. (Address: Dr. L. D. MacLean, Surgeon-in-Chief, Royal Victoria Hospital, Montreal 2, Quebec, Canada.)

The umbilical vein is patent but collapsed in adults. There is a valve at the entrance of the umbilical vein to the left branch of the portal vein. The technique of isolating and catheterizing the umbilical vein is presented. A liver biopsy is done at the same time as the catheterization. The catheter is left *in situ* for up to 4 days. Manometric and hepatoportographic studies are subsequently done.

Umbilical vein catheterization and hepatoportography were attempted in 30 patients by the authors and were successful in 22. The umbilical vein was stenosed in 1 of the 8 failures and was compressed by tumor, extensive hepatic regeneration and scarring in cirrhosis, or because it had been ligated in the other failures.

Hepatoportographic studies were done using renografin 76. The catheter was checked by image intensification fluoroscopy. A synchronized pressure injector and a rapid film changer were used.

The normal hepatogram shows two phases. The angiogram phase outlines the hepatic portal tree and lasts from 3 to 5 seconds. The flush phase outlines the liver and lasts from 6 to 12 seconds. The liver normally clears the contrast medium within 15 seconds.

Umbilical vein hepatoportography was found to be useful in the study of portal hypertension, suspected intrahepatic tumors or abscesses, unexplained hepatomegaly, unsuspected anomalies and hepatic and parahepatic masses.

Several illustrative cases are presented. There was a retrograde flow of the contrast medium and visualization of the extrahepatic tree including the splenic and mesenteric branches in portal hypertension. A mottled appearance of the liver was seen in early cirrhosis between the angiogram and flush phases due to scarring and regeneration. Intrahepatic tumors produced a displacement of the portal vasculature during the angiogram phase and a nonopacified radiolucent defect during the flush phase.

Umbilical vein hepatoportography was found to be an important procedure in the diagnosis of liver lesions.—*Charles W. Cooley, M.D.*

WATT, J. KENNEDY. Pattern of aorto-iliac occlusion. *Brit. M. J.*, Oct. 22, 1966, *2*, 979–981. (From: Glasgow Royal Infirmary, and Peripheral Vascular Unit, Belvidere Hospital, Glasgow, Scotland.)

The author reports on 100 aortograms in which occlusions producing intermittent claudication were found. From this study 3 common sites of origin for aorto-iliac occlusions were identified.

In 34 cases the arterial lesion originated at the aortic bifurcation. This usually produces stenosis of the orifices of both common iliac arteries. Various degrees of stenosis with or without thromboembolic occlusion may be seen. When both common iliac arteries are occluded, thrombus may extend proximally as far as the origin of the inferior mesenteric artery.

In 31 cases the arterial lesion originated in the common iliac artery. This is the most common vessel to be occluded, usually by lesions originating in any of the 3 common sites. The lesions are frequently

bilateral but not necessarily synchronous; they may progress to bilateral common iliac and then aortic occlusions which makes determination of the origin of the lesion difficult.

Twenty-eight cases revealed the origin of the arterial lesion to lie at the common iliac bifurcation and this was most commonly associated with occlusion of the external iliac artery, which extended to involve the inferior epigastric artery leaving the common femoral artery patent. Occlusions of the common femoral artery are usually associated with a patent external iliac artery. Internal iliac artery occlusion causes buttock claudication but rarely is an isolated lesion, it usually being associated with combined lesions.

Combined lesions of the common, external, and internal iliac arteries are rare; usually common and external iliac artery lesions are found. Generally, collaterals develop early and maintain patency of the internal iliac artery where vessels originate proximal near its bifurcation. The common iliac and external iliac arteries have no major proximal branches and subsequently are prone to secondary occlusion.

In the lower extremity arterial lesions develop at bifurcation sites, in relation to a fixed unyielding tendon or in an artery with large curves and large branches. The common iliac artery is subject to none of these preconditions. In combined lesions platelet thrombi form at the bifurcation but leave the proximal 2.5 cm. free from deposits. Linear deposits again accumulate distal to this free zone. This would approximate the middle of the common iliac artery. In isolated lesions an atherosclerotic elongated aorta will pulsate in an up-and-down manner with each pulsation. Since the aorta is anchored proximally by the renal and superior mesenteric arteries and distally by the origin of the internal iliac artery with its many branches, the middle of the common iliac artery buckles and develops intimal hyperplasia with subsequent plaque formation.

The femoral and popliteal arteries were patent in 56 cases. The patency was more common in the more proximal lesions. The explanation for this interesting fact appears to lie in the protective effect of the lower distal arterial pressure.—*James R. Stevenson, Captain, MC*

Craig, Oscar, and Snell, Michael. External iliac vein obstruction. *Brit. J. Surg.*, Aug., 1966, *53*, 668–671. (From: St. Mary's Hospital, London, and Harefield Hospital, Middlesex, England.)

The authors find that an essential part of phlebography of the lower extremities is to demonstrate the whole deep venous systems including the iliac veins.

Ascending phlebography, using controllable compression cuffs, is recommended as the method of choice in such investigations.

Four patients are reported with external iliac vein obstruction. The patients complained of one or all of the following: leg edema, varicose veins, eczema, and ulceration.

Obstructive effects of a distended bladder on the veins of the pelvis were seen in 1 case.—*George A. Miller, M.D.*

Braun, Esmond. Hemothorax after translumbar aortography. *J. Urol.*, Aug., 1966, *96*, 263–264. (From: Department of Surgery, Wayne State University School of Medicine and Dearborn Veterans Administration Hospital, Detroit, Mich.)

Hemorrhage into the pleural space after trans lumbar aortography is a rare and serious complication of this diagnostic procedure.

This is a case report of a 38 year old hypertensive male who experienced such a complication. A translumbar needle was placed in the aorta at about the level of the 11th thoracic vertebra. Immediately after the hand injection of 20 cc. of sodium diatrizoate, the patient experienced severe left chest pain. His blood pressure and pulse remained near normal. Physical signs of fluid developed in the left chest, and a roentgenogram made 3 hours later showed a large hemothorax. The serial exposures of aortography revealed extravasation of opaque medium into the extrapleural and pleural space. Eight hundred cc. of blood was removed by needle aspiration and the following day another 425 cc. was aspirated. The patient recovered and no further hemothorax developed.

The author classifies the complications of abdominal aortography in 4 divisions; namely visceral injuries, atopic reactions, hemorrhage, and injuries due to displacement of the needle during injection.

It is interesting that 2 previous cases of similar intrapleural hemorrhage were in hypertensive individuals, and the needle placement was above the 12th vertebral body. In 1 of the previously reported cases it was necessary to do an open thoracotomy and a suture repair of the aortic perforation.—*George W. Chamberlin, M.D.*

Hoar, Carl S., Jr., Wheelock, Frank C., Jr., Kellett, Mirle, Koch, Gert, and Guggenheim, Wolf. Experience with femoral arteriography in diabetic peripheral vascular disease. *Surg., Gynec. & Obst.*, Oct., 1966, *123*, 826–833. (From: New England Deaconess Hospital, Boston, Mass.)

Two hundred and ninety-four femoral arteriographies on 245 diabetic patients with peripheral vascular disease over a 6 year period were reviewed. The majority of the patients had gangrenous foot lesions; the remainder had ischemic pain or claudication. Most had other manifestations of diabetes such as neuropathy, nephropathy or retinopathy, as

well as evidence of coronary disease. Patients were selected for examination if restorative surgery to heal a gangrenous lesion or make a minor amputative procedure successful was contemplated.

All patients were classified according to Haimovici (Am. J. Roentgenol., Radium Ther. & Nuclear Med., 1960, *83*, 1042), depending upon the area involved, the extent of occlusive disease, and the status of collateral and runoff vasculature. In addition, the cases were graded from 1 to 4 according to surgical feasibility.

On the basis of the arteriographic findings, 98 reconstructive procedures were performed with 60 absolute and 10 relative successes. The majority of the successful results were in those graded 1 and 2. One hundred and sixty-two amputations were performed, the extent of surgery and the degree of success correlating somewhat with the arteriographic grading. It was felt that without arteriography the correct procedure could not be selected with the high degree of accuracy necessary to prevent unrewarding surgery in an already bad situation.—*Mark D. Reiss, M.D.*

RADIOISOTOPES

Burke, Gerald, and Halko, Arlene. Dynamic clinical studies with radioisotopes and the scintillation camera: II. Rose bengal I^{131} liver function studies. *J.A.M.A.*, Nov. 7, 1966, *198*, 608–618. (Address: Dr. Burke, 2929 S. Ellis Avenue, Chicago, Ill.)

A scintillation camera with a 11.5 inch diameter sodium iodide (thallium activated) crystal was used to study liver function with rose bengal I^{131}. The camera was positioned to include the inferior cardiac blood pool, the liver and the infrahepatic area of the abdomen. A dose of 0.7 μc per pound of body weight was injected and scintiphotos were made at 5 minute intervals for 1 hour, and at hourly intervals if needed. The scintiphotos were studied in sequence regarding: (1) time at which the decline in blood radioactivity plateaued; (2) time at which maximum hepatic radioactivity occurred; (3) magnitude and distribution of maximal hepatic isotope uptake; (4) first appearance time of radioactivity in the common bile duct or intestine, or both; and (5) rate or magnitude of biliary or intestinal isotope excretion, or both.

Twenty patients with no clinical or biochemical evidence of liver disease were studied. The cardiac blood pool reached a minimum at 30 minutes, the maximum hepatic uptake was at 20 minutes, and the first detectable biliary excretion was at 20 minutes. Activity was demonstrated in the gastrointestinal tract at 25 minutes, but it was not until 35 to 40 minutes that the common bile duct was well outlined and there was a significant amount of activity in the gastrointestinal tract.

Three cases of extrahepatic obstructive jaundice were studied. There was a normal rate of decline in blood radioactivity, a sustained increase in intrahepatic isotope accumulation, and no discernible biliary or gastrointestinal isotope excretion.

Five patients with significant intrahepatic cholestasis were studied, and in each case there was a delayed but definite biliary and gastrointestinal excretion.

Fourteen cases were studied to correlate the biochemical indices of liver function and the rose bengal I^{131} scintiphoto test, and the correlation was found to be generally satisfactory. The number of cases, however, precluded a definite assessment of the correlation.

The scintiphoto study is better than the double probe study, as it eliminates the error in placement of the abdominal probe and the large crystal is more efficient and sensitive in monitoring biliary excretion of the labeled dye in the presence of severe hepatocellular disease.

The scintillation camera rose bengal I^{131} liver function study is of significant value in differentiating extrahepatic biliary tract obstruction from intrahepatic jaundice, as it provides constant visual monitoring of hepatic uptake of labeled dye from the circulation and its excretion into the biliary tree and intestine. This test is a useful adjunct in the clinical assessment of hepatic dysfunction and warrants further investigation.—*Charles W. Cooley, M.D.*

Rosenthall, Leonard, and Usher, Michael S. Assessment of combined frontal and lateral views in liver scanning. *J. Canad. A. Radiologists*, Sept., 1966, *17*, 151–154. (From: Department of Radiology, Montreal General Hospital, Montreal, Quebec, Canada.)

The radionuclide liver scan has been used to evaluate gross hepatic morphology and especially in patients with questionable hepatic metastases. The scattered radiation and distance from the detector probe limit the size of a lesion that can be detected. Lateral and posterior scans in addition to the frontal scan have yielded additional information.

The authors used a conventional rectilinear scanner for the frontal scans and a gamma-ray scintillation camera set for the accumulation of 80,000 counts for the lateral scans. The scannings were done 1 hour after the intravenous injection of 200 μc of colloidal Au^{198}.

The scans were numbered and the frontal and lateral scans were examined separately, the impressions were recorded, and then the frontal and lateral scans were examined together. Forty-four abnormal liver scans were found in 385 cases using the combined scans. The lateral scan reduced the number of false negatives by 20 per cent; in 30 per cent of the cases the frontal scan was suspicious and the lateral scan was definitely abnormal.

The lateral scan was found to be helpful in sug-

gesting the presence of biliary tract disease, in differentiating between tumor and cirrhosis, and in localizing subphrenic abscesses.—*Charles W. Cooley, M.D.*

Holmes, Richard A., Silbiger, Martin L., Karmen, Arthur, Wagner, Henry N., Jr., and Stern, Howard S. Cardiac scanning with technetium-99m-labeled albumin. *J.A.M.A.*, Oct. 3, 1966, *198*, 67–72. (Address: Dr. Holmes, 615 N. Wolfe Street, Baltimore, Md. 21205.)

Fifty-nine cardiac blood pool scannings were made by the authors using 2–4 mc technetium 99m tagged human serum albumin. The resolution and the structural details were greatly improved and certain anatomic structures not previously visible by other radioactive substances became visualized.

Also, cardiac blood pool scans with radioactive pertechnetate were compared with Tc^{99m} labeled albumin in the same patients and it became obvious that Tc^{99m} tagged serum albumin produced better resolution and proved to be, at present, the material of choice for blood pool scanning.—*Abbas M. Rejali, M.D.*

Fawwaz, R. A., Winchell, H. S., Pollycove' M., Sargent, T., Anger, H., and Lawrence' J. H. Intestinal iron absorption studies using iron-52 and Anger positron camera. *J. Nuclear Med.*, Aug., 1966, *7*, 569–574. (From: Donner Laboratory, University of California, Berkeley, Calif.)

The authors describe the use of iron 52 and the Anger positron camera in the study of iron absorption by the gastrointestinal tract.

In this technique, the rate of absorption of orally administered iron into the plasma as a function of time is correlated with its distribution in the gastrointestinal tract.

Six normal subjects have been studied and all showed similar rates of absorption of labeled substance which correlated with its distribution in the gastrointestinal tract.

The maximal rate of intestinal iron absorption in humans occurs when orally administered iron is present in the stomach and upper small intestinal tract. The slow phase of iron absorption appears to be the result of retention of part of the orally administered iron in the jejunal area.—*Abbas M. Rejali, M.D.*

McCartney, R., Kerr, R. C., Cass, N. M., and van den Brenk, H. A. S. Blood flow in limbs determined with ^{131}I-HSA after application of tourniquets to deliver radiation under anoxic conditions in sarcomata of the extremities. *Australasian Radiol.*, Aug., 1966, *10*, 240–242. (From: Physics Department, Hyperbaric Oxygen and Radiobiological Research Units, Cancer Institute Board, Melbourne, Australia.)

If large doses of radiation are delivered to tumors of the extremities previously rendered hypoxic, severe tissue damage may result if the arrest of blood flow is inadequate and allows small quantities of unmetabolized oxygen to remain in the normal tissues during irradiation. Polarographic techniques, measuring tissue oxygen tension, and temperature measurements have been used to determine the efficacy of the tourniquet in producing tissue hypoxia. This study concerns the use of radioiodinated human serum albumin (I^{131} HSA) injected intravenously in 2 patients 5 minutes after application of a tourniquet, with subsequent measurement of radioactivity distal to the tourniquet.

In both patients some blood was demonstrated to enter the limb, presumably via nutrient vessels feeding the noncompressible bone marrow, but this only was approximately one-tenth that of the control limb. The amount of flow seemed to increase when the limb was heated, but muscle tetanization produced no change. Both these techniques are used in an effort to promote oxygen utilization and facilitate tissue anoxia.

Although significantly measurable flow occurs past a tourniquet, the amount appeared insufficient to alter marked radiobiologic protection of normal tissues. The need for precautionary measures to ensure adequate circulatory arrest in the face of radiation doses which would certainly produce necrosis in normally oxygenated tissue is stressed.—*Mark D. Reiss, M.D.*

Cantolino, S. J., Schmickel, R. D., Ball, M., and Cisar, C. F. Persistent chromosomal aberrations following radioiodine therapy for thyrotoxicosis. *New England J. Med.*, Oct. 6, 1966, *275*, 739–745. (From: The Cytogenetics Section, Research Branch, Division of Radiological Health, United States Public Health Service, Rockville, Md.)

The authors state that evidence indicates that human chromosomes are at risk when they get exposed to ionizing radiation.

To establish the effect of ionizing radiation, a long term study of the chromosomes of peripheral leukocytes in 5 adult female patients who were treated with I^{131} for hyperthyroidism was made. All received a therapeutic dose and subsequently had to be considered separate for evaluation of the data.

A control venous blood specimen was obtained from the 5 patients serving as their own pretreatment controls as well as from 12 normal subjects. At 7 different intervals, from 2 hours to 1 year after

treatment with I^{131}, about 3,500 cells were studied and scored for chromosomal aberrations.

A significant number of chromosomal aberrations were noted in all subjects who received a single therapeutic dose of radioactive iodine, including rings, dicentric and acentric fragments at all intervals up to and including 1 year after treatment. These aberrations were not diminished after 1 year.

No definite correlation between the level of radioactive iodine in the plasma and incidence of aberration was noted in these subjects, and none showed a peak incidence aberration from 2 hours to 1 year. Higher incidence of rings was noted in the patients who received 2 additional treatments.

It is concluded that persistent chromosomal aberrations can follow radioiodine therapy for thyrotoxicosis, and that radioiodine therapy for thyrotoxicosis can produce significant and persistent chromosomal aberrations in peripheral leukocytes.—*Abbas M. Rejali, M.D.*

CHEMOTHERAPHY

Dameshek, William, Necheles, Thomas F., and Finkel, Harvey E. Survival in myeloblastic leukemia of adults. *New England J. Med.*, Sept. 29, 1966, *275*, 700–702. (From: Blood Research Laboratory, New England Medical Center Hospitals and the Department of Medicine, Tufts University School of Medicine, Boston, Mass.)

As survival in myeloblastic leukemia of adults has not appreciably changed since the advent of chemotherapy, it has been suggested that aggressive chemotherapy with combination of agents might prolong life in this disease. With this idea in mind, the record of 65 patients seen by the authors in the past 2½ years were reviewed.

The combination therapy consisted of prednisone, 6-mercaptopurine, vincristine, and occasionally amethopterin.

The age of the patients varied from 15 to 79 years, with a median of 53 years.

This study indicated that survival in myeloblastic leukemia in adults is highly variable, with a significant portion of patients living for more than 1 year after diagnosis without specific therapy. Although individual patients may be benefited by aggressive combination therapy, in general this was not found to be true. Indeed, survival in some cases is probably shortened by overenthusiastic treatment.

In conclusion, the authors state that they doubt whether any presently available set of antileukemia agents represents any significant advance in the clinical management of this disease.—*John H. Harris, M.D.*

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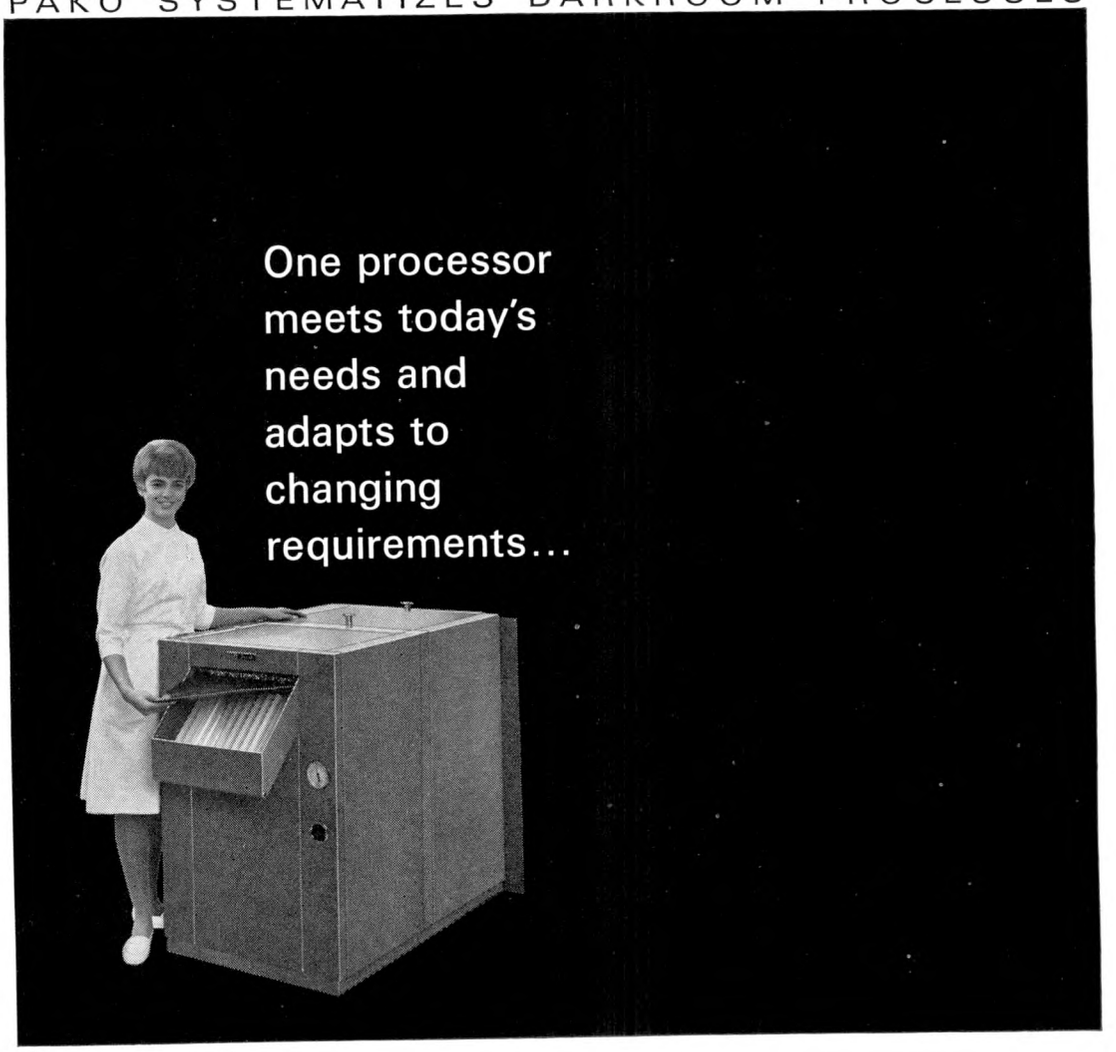
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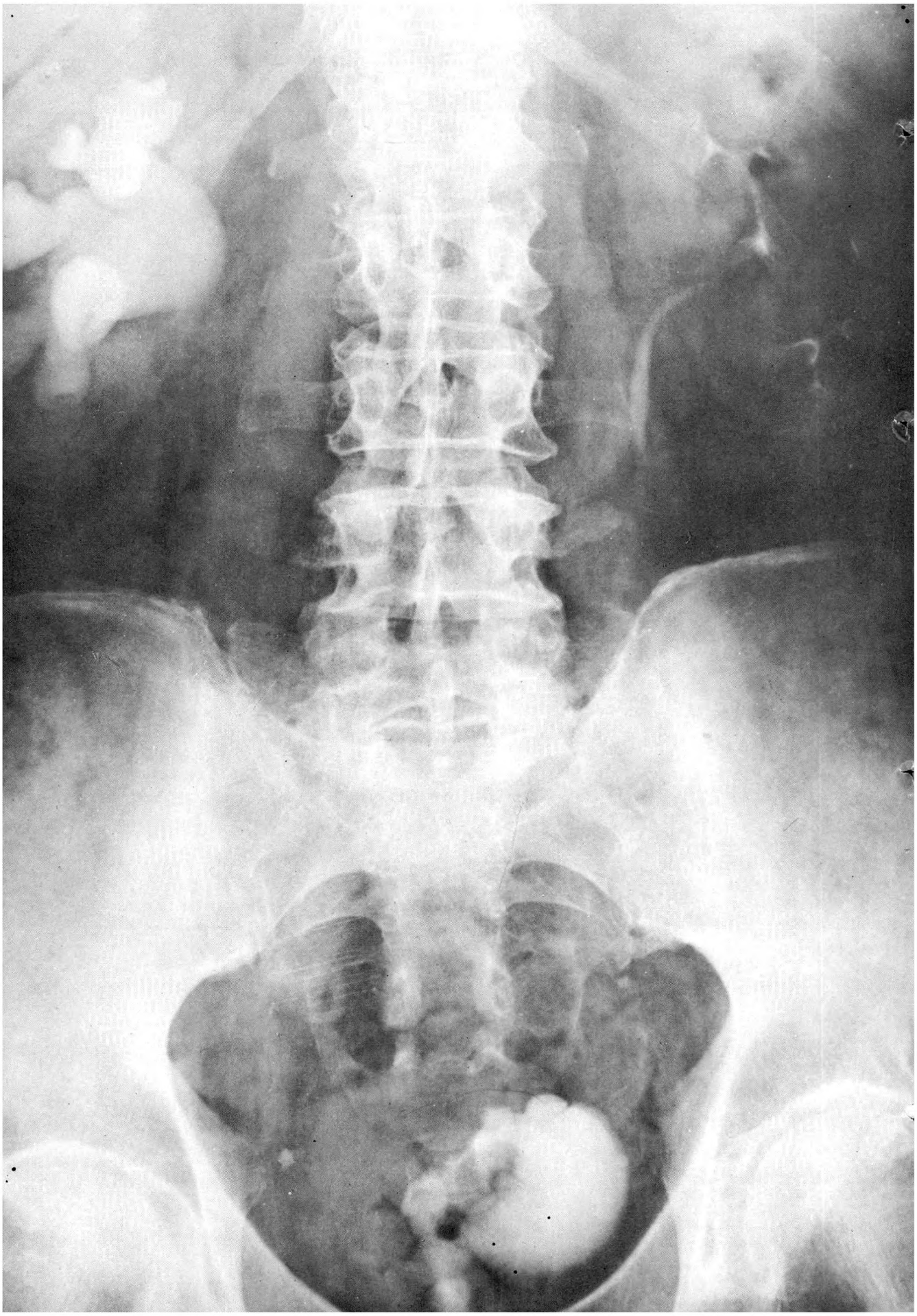
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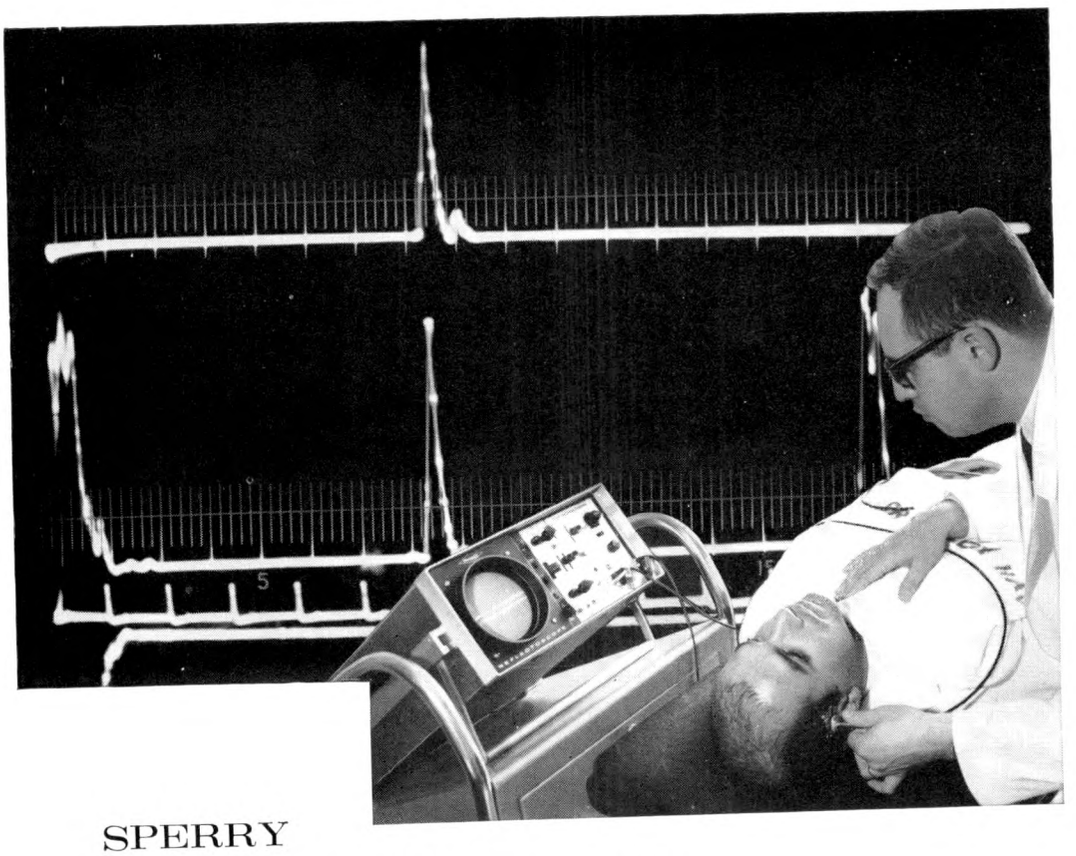
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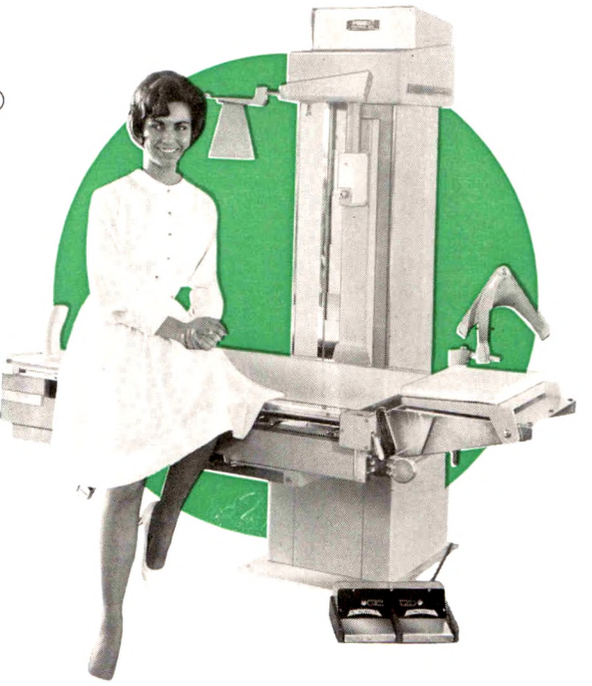
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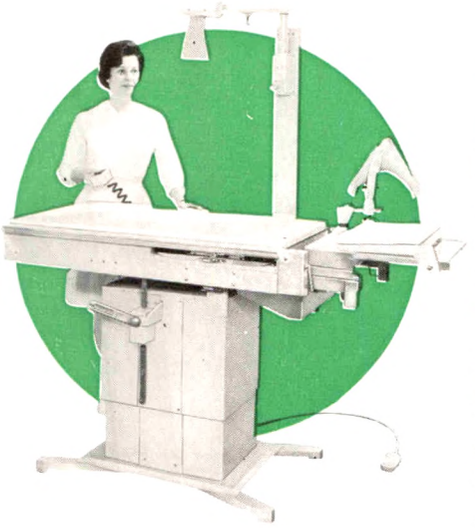
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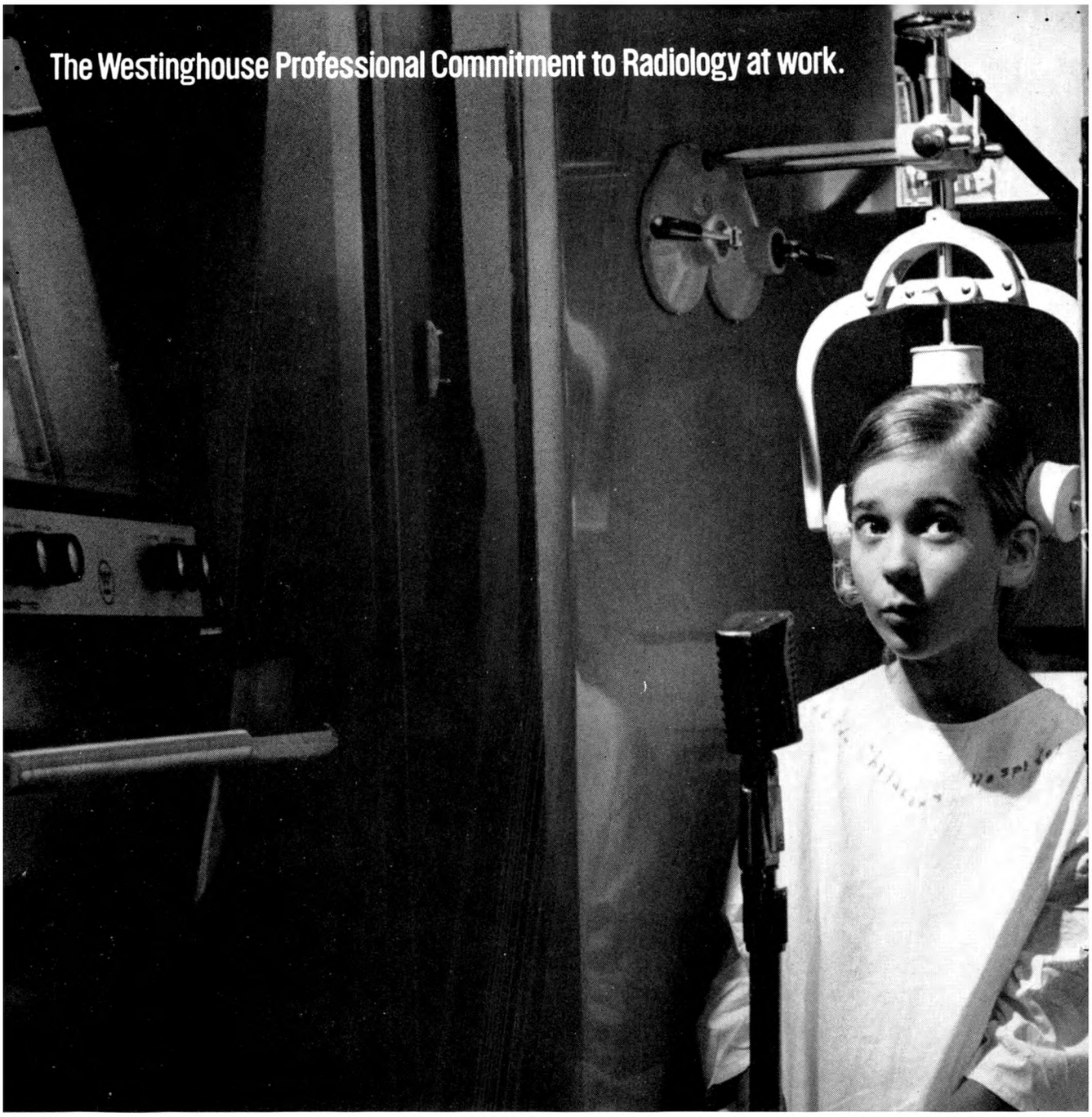
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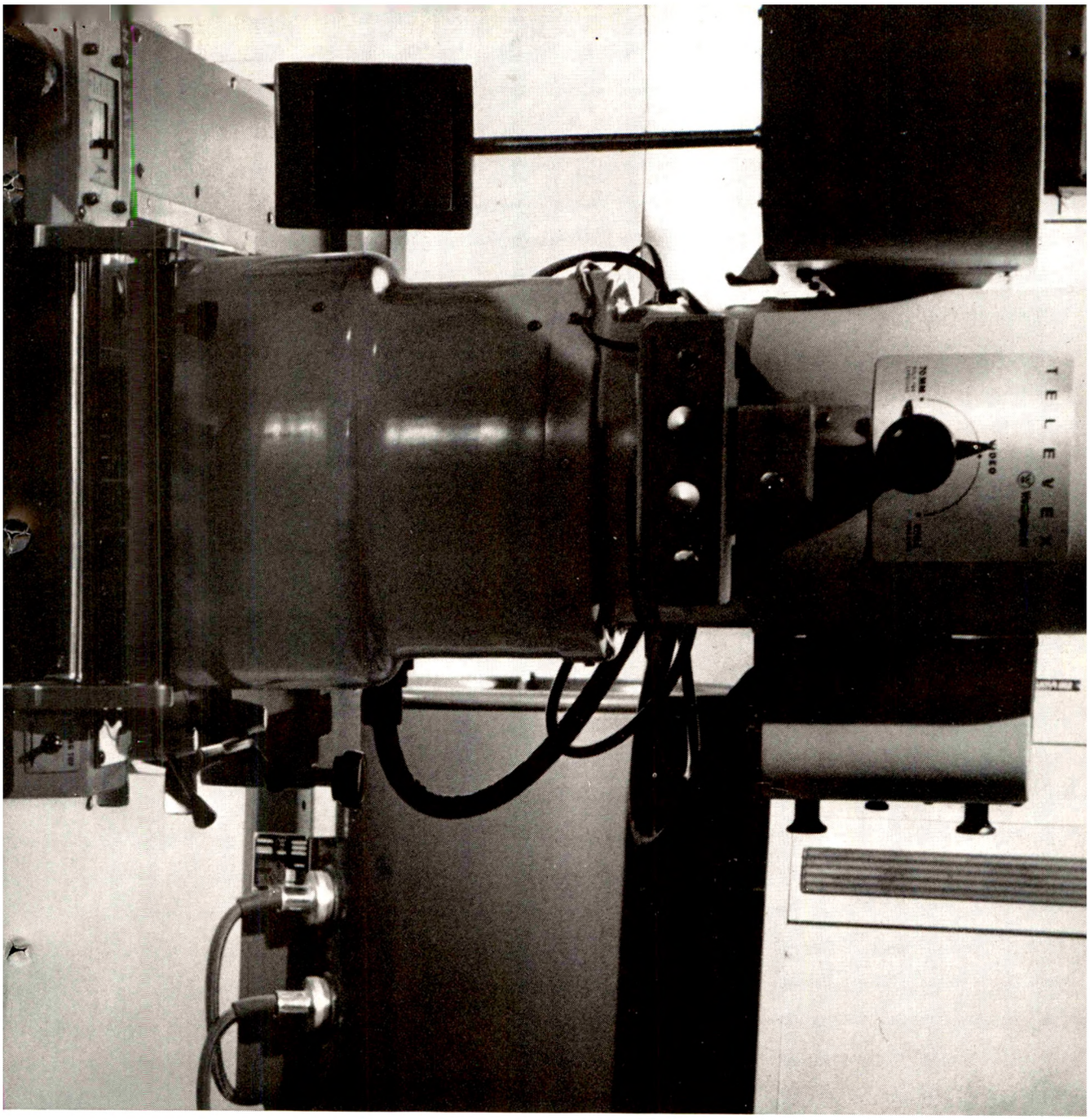
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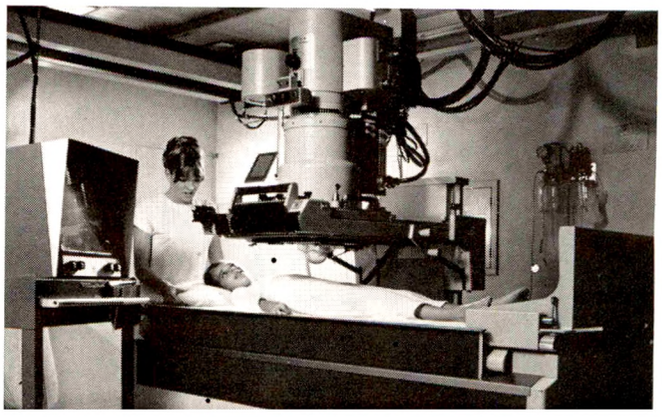
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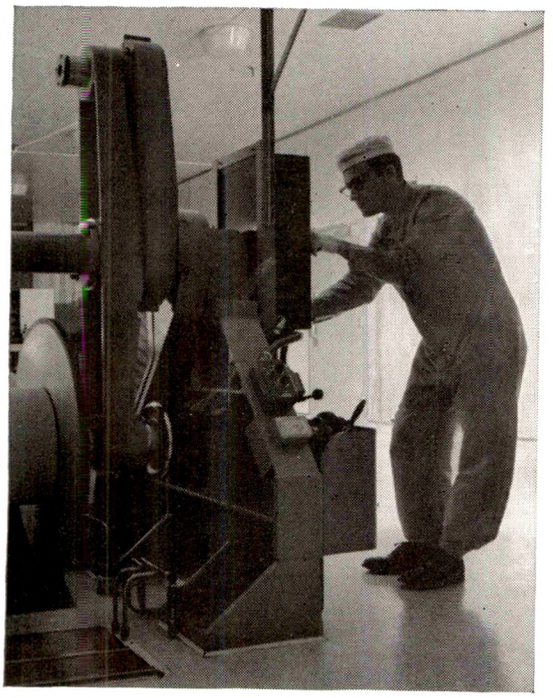
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*Margulis, A. R., and Heinbecker, P.: Am. J. Roentgenol. *86*:103 (July) 1961.

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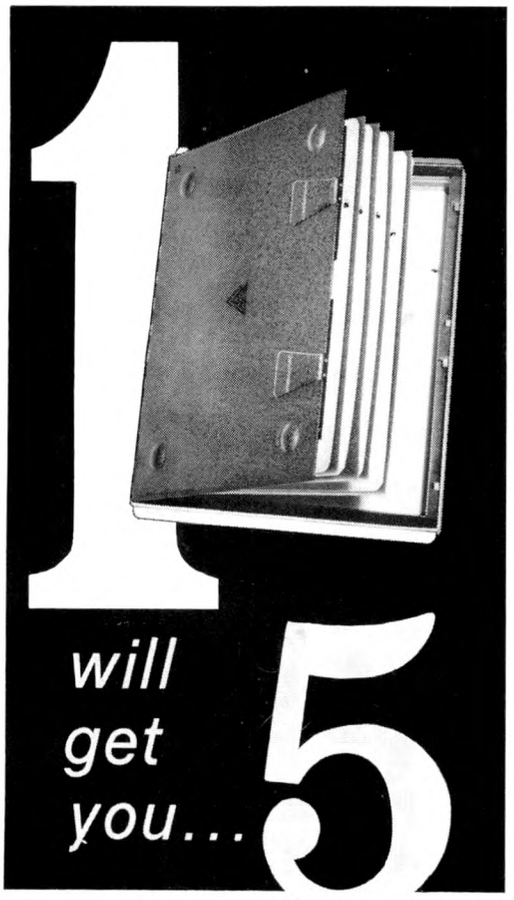
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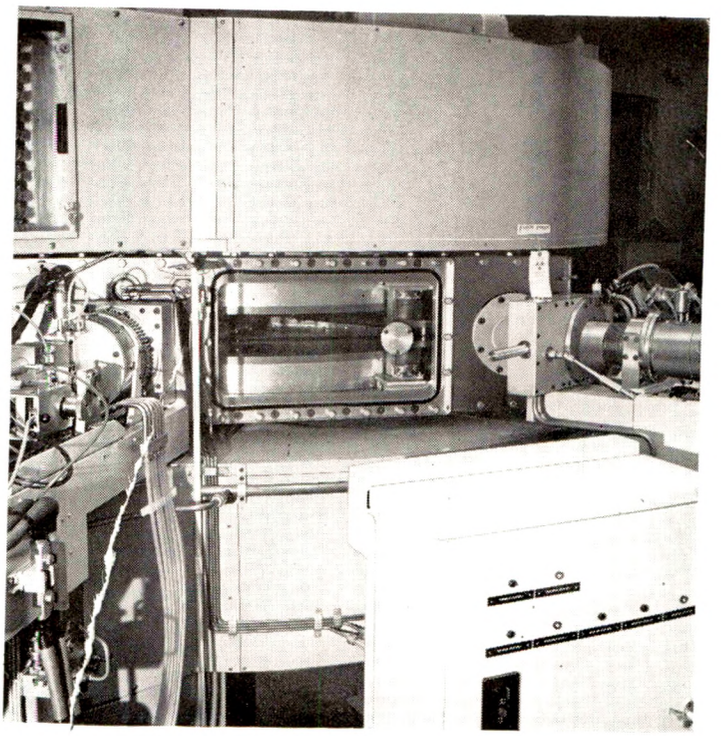
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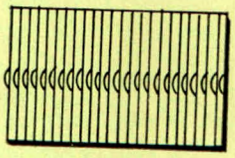
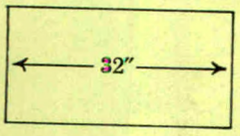
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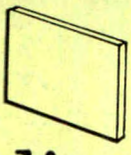
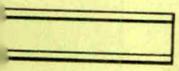
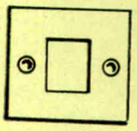
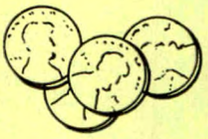
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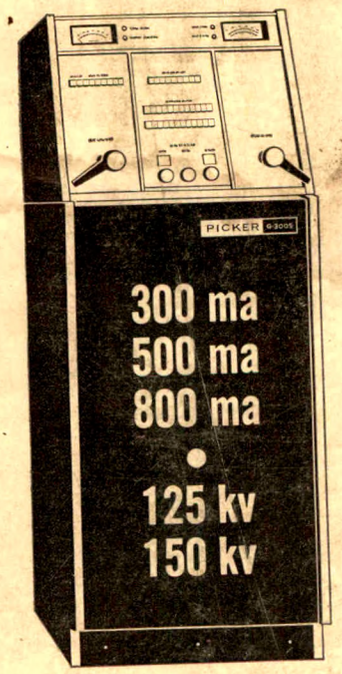
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   (There is a model for every room)
4. **can "take it"**
   (Built to minimize downtime)

Ask your local Picker representative for details or write Picker X-Ray Corporation, White Pla